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# Handbook of Pharmaceutical Granulation Technology

edited by

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## Preface

Granulation of powders to produce a pharmaceutical solid-dosage form is an essential unit operation. The process of enlarging particles is carried out elsewhere, such as in the food, agrochemical, dyestuff, and chemical industries, to produce from fine powders free-flowing, dust-free granules for further processing. Granulation in the pharmaceutical industry poses unique challenges, as it has the additional requirements of content uniformity and consistent physical properties, such as particle size, moisture, bulk density, porosity, hardness, and compressibility. Production of pellets for controlled-release application, which employs similar technology, requires pellets to be of consistent density, size, porosity, and surface morphology.

Regulatory requirements in the pharmaceutical industry have created the need for an understanding of this unit operation at an early stage of product formulation, method selection, and process development. Because the processes and specifications for the pivotal test batches and full-scale production "must be equivalent," the need for reliable control of the manufacturing process used to produce the test and clinical batches cannot be overemphasized. Drug substance characterization, granulation analysis, dose uniformity, and dissolution profile are the key controls that should be in place at an early stage.

In the past 20 years, the pharmaceutical industry has been introduced to a number of different methods for producing pharmaceutical granulation. These methods have offered a number of advantages, such as process efficiency, while addressing product quality and regulatory compliance.

The current climate in the pharmaceutical marketplace has created economic challenges for the industry, which must constantly comply with current FDA regulations and policy. Because pharmaceutical granulation is



a critical unit operation in the manufacture of solid-dosage forms, cost-effective methods have been sought by the industry. Besides the FDA, other regulatory authorities, such as OSHA and EPA in the United States, are concerned about the safety of employees who handle and granulate "potent" compounds. These concerns have resulted in the development of "contained" systems. Potent compounds can now be granulated in so-called one-pot systems, which offer a greater measure of safety to the operator by providing a single "pot," or bowl, to granulate and dry the product. Another approach to containment is the use of an integrated granulating plant comprising various process equipment that requires minimal or no handling by the operator as the product goes through the granulation steps.

Another trend in the pharmaceutical industry is the move toward continuous granulation of pharmaceuticals. Roller compactor units have long provided a method to produce dry granulation for some products, but availability of compact units for wet granulations is now a reality. These units provide economic advantages, while providing easy scalability from pilot-size batches to production-size lots.

Pharmaceutical granulation technology continues to change. Economic and regulatory forces make it mandatory to select cost-effective, safe methods for production of pharmaceutical granulation. The method selected must meet stringent regulatory requirements to produce a product with the desired characteristics and consistency.

This book is designed to give readers comprehensive knowledge of the subject. An appropriate level of theory has been incorporated to provide fundamentals of powder characterization, granulation, and state-of-the-art technology. However, the emphasis is on the application of these basic principles to the industrial practice of producing pharmaceutical granulation. The new technologies employed in the industry and contemporary approaches to producing pharmaceutical granulation are important areas covered in this book.

Pharmaceutical professionals, such as research and development scientists, process engineers, validation specialists, process specialists, and quality control scientists, will find the level of theory appropriate and the wealth of practical information invaluable for selecting and using each method, while keeping in mind regulatory requirements and cost effectiveness.

I sincerely acknowledge the support of the contributing authors of this book and thank them. Their timely submission of manuscripts greatly expedited publication. My heartfelt gratitude goes to my colleagues at Niro Inc. (parent company of Atlantic Pharmaceutical Services Inc.) for their help, and special thanks go to Mr. Steven M. Kaplan, President, and Mr. Steven A. Lancos, Executive Vice President of Niro Inc., for their support and encouragement during the preparation of this book.

*Dilip M. Parikh*

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# 1

## Introduction

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The granulation process of size enlargement used within the pharmaceutical industry has its roots in ancient times. Perry's Chemical Engineer's Handbook [1] defines the granulation process as "any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified." This definition is of course particularly appropriate to a pharmaceutical granulation where the rapid breakdown of agglomerates is important to maximize the available surface area and aid in solution of the active drug.

The practice of delivering medicinal powder by hand rolling into a pill by using honey or sugar has been used since ancient times. It is still a practice to deliver the botanical and herbal extract in Ayurvedic and homeopathic branches of medicine. The term "granulated" material is derived from the Latin word "granulatum," meaning grained. The granulation material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. In modern times, granulation

**Table 1** Most Frequently Used Pharmaceutical Granulation Techniques

Wet granulation	Drying
1. Low shear mixer	Tray or fluid bed
2. High shear mixer	Tray or fluid bed
3. High shear mixer	Microwave assist/vacuum/gas stripping
	One pot processing
4. Fluid bed granulator	Fluid bed
5. Spray dryer	Spray dryer
6. Extrusion/spheronization	Tray or fluid bed
7. Continuous mixer granulator (mechanical)	Fluid bed (batch or continuous)
8. Continuous fluid bed granulator	Fluid bed (continuous)
<b>Dry granulation</b>	
1. Direct compression	Blend and process further
2. Slugging	Compress/mill/screen/blend/process further
3. Roller compactor	Compacts/mill/blend/process further

technology has been used by a wide range of industries, such as coal, mining, and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling and enhance the material's ultimate utility. Granulation methods can be divided into two types: wet methods which utilize a liquid in the process, and dry methods in which no liquid is utilized. Both of these methods are utilized in the pharmaceutical industry, however, wet granulation technology is the more common (see Table 1).

The development of pharmaceutical granulation was driven by the invention of the tablet press by W. Brockedon in 1843. Subsequent improvements in the tablet machinery was patented in the United States by J. A. McFerran (1874), T. J. Young (1874), and J. Dunton (1876). The demands on the granulation properties were further enhanced in the 1970s as high speed tablet machines with automated controls were introduced.

Pharmaceutical granulations are used primarily for the preparation of materials for tableting. To a lesser extent they are used as a precursor to the encapsulation process. In some applications the process is used to produce spherical granules for the modified release indications or to prepare granules as sprinkles to be used by the patients directly. The reasons for granulating a pharmaceutical compound are listed below:

1. To increase the uniformity
2. To densify the material
3. To enhance the flow
4. To facilitate metering
5. To reduce dust
6. To improve the appearance

Successful processing depends on proper control of the process. To encourage agglomerate formation, mechanical strength in the product, the system can be critical to the densification of the agglomerate, and the structure appropriate to the end use.

The compression of drugs without going through the granulation process is a directly compressible formulation. It has many advantages, such as low cost, efficient operation involving less equipment, and no compression. In the 1970s microencapsulation vehicle was introduced. The use of crystalline cellulose is suitable for many compounds are capable of being compressed. The recent trend in the technology, in which the drug substance is in liquid, and spray dried to produce a powder, can be compressed after the drying process. These are substances of poor self-compressibility or incompatibility with the spray drying process. The granulation process is essential for these substances.

Dry compaction technique is used for a limited number of applications. The technology development employed in the past which were meant for mixing and blending. This technology is still being used, but it is not the most efficient process. The newer generation of process is being developed, which is desirable now, because of its ease of process control capabilities. The newer technologies, such as one pot process, then dry by either using vacuum or fluid bed in the same vessel. Fluid bed

# ical Granulation Techniques

## Drying

Tray or fluid bed  
 Tray or fluid bed  
 Microwave assist/vacuum/gas stripping  
 One pot processing  
 Fluid bed  
 Spray dryer  
 Tray or fluid bed  
 Fluid bed (batch or continuous)  
 Fluid bed (continuous)

Blend and process further  
 Compress/mill/screen/blend/process further  
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 elow:

1. To increase the uniformity of drug distribution in the product
2. To densify the material
3. To enhance the flow rates and rate uniformity
4. To facilitate metering or volumetric dispensing
5. To reduce dust
6. To improve the appearance of the product

Successful processing for the agglomeration of primary particles depends on proper control of the adhesional forces between particles, which encourage agglomerate formation and growth and provide adequate mechanical strength in the product. Furthermore, the rheology of the particulate system can be critical to the rearrangement of particles necessary to permit densification of the agglomerate and the development of an agglomerate structure appropriate to the end-use requirements.

The compression of drug substance with the excipients can be achieved without going through the granulation steps. By simply mixing in a blender, a directly compressible formulation can be processed. This has several obvious advantages, such as lower equipment cost, faster process time, and efficient operation involving only two steps, namely, blending and compression. In the 1970s microcrystalline cellulose as a directly compressible vehicle was introduced. The compressible formulation containing microcrystalline cellulose is suitable for a number of products. However, not all compounds are capable of being processed as a direct compression formulation. The recent trend in the industry is to evaluate spray drying technology, in which the drug substance and the excipients are incorporated in a liquid, and spray dried to produce free flowing powder. The resultant powder can be compressed after the lubrication addition and blending steps. There are substances of poor self-compressibility, low solubility, high drug content, or incompatibility with the spray drying process. For such compounds the granulation process is essential.

Dry compaction techniques such as slugging or roller compaction are used for a limited number of products. Early stages of wet granulation technology development employed low shear mixers, such as ribbon mixers which were meant for mixing dry powders. The same low shear granulation technology is still being used for a number of products, even though it is not the most efficient process and lacks process controls common in the newer generation of process equipment. The high shear granulation is desirable now, because of its efficient and reproducible process and modern process control capabilities. The high shear mixers have also facilitated new technologies, such as one pot processing, that use the mixer to granulate and then dry by either using vacuum, gas stripping/vacuum, or microwave assist in the same vessel. Fluid bed processors have been used in the pharmaceu-

tical industry for the last 30 years, initially only as a dryer, and now as a granulator and a particle coater. A high shear mixer can be placed in line with a fluid bed processor. After the mixture is granulated in a high shear mixer, the densified wet mass is transported to the fluid bed dryer to dry. These two unit operations and the transfer between them can be controlled by a single process controller. Such a system optimizes containment, minimizes material handling requirements and reduces the foot print required for these units. Extrusion/spheronization is used to produce granulation for tabletting or pelletizing which involves mixing, extruding, spheronizing, and drying unit operations.

Efficient and cost effective manufacturing of pharmaceutical products is being evaluated by the scientists, engineers, and operational managers of pharmaceutical companies due to the current health care environment in the United States. The primary driver is cost containment, demanded by powerful group purchasers of health care that will no longer accept steadily rising pharmaceutical prices such as the 9.6% average annual compound rate recorded during the 1980s. Demands for price restraint also extends to Europe; government-backed pharmaceutical payment plans in Germany and Italy, for example, have cut back reimbursements. Acquisitions remain the preferred route to quickly enhance a product portfolio. The result is an unprecedented rise in mergers and acquisitions in the pharmaceutical industry. Table 2 shows major mergers and acquisitions that have taken place since 1983. This trend of merging of the equals or takeover of the significant technological companies will continue. Major pharmaceutical companies are witnessing the end of traditional research and development. Drug delivery companies are becoming potential targets for mergers or strategic alliances. During all the upheaval that the industry is going through, it is becoming obvious that the cost of development and production must be controlled. The efficiencies that were not necessarily sought after are becoming the first priority of the pharmaceutical companies. The manufacturing of solid dosage products is no exception.

The significant advances that have taken place in the pharmaceutical granulation technology are presented in this book to provide the readers with choices that are available. There is no substitute for good science. The characterization of the drug substance along with knowledge of granulation theory and a good definition of the end product required will prepare the reader to explore the various options presented in this book. Each drug substance poses a unique challenge that must be taken into consideration at the process selection stages by the researchers. The various techniques presented in this book will further help the scientist in their understanding and selection of the granulation process most appropriate for the drug substance. For production and engineering professionals in the industry, this book is intended

**Table 2** Recent Mergers and Acquisitions in the Pharmaceutical Industry

Year	Mergers and Acquisitions
1983	Rhône-Poulenc and Rorer
1985	Rorer and USV/Armour
1985	Monsanto and Searle
1986	Schering and Key Pharmaceuticals
1988	Kodak and Sterling
1989	Dow Chemical and Marion
1989	Bristol-Myers and Squibb
1989	American Home Products and Pharmacia
1990	Pharmacia and Kabi
1990	Boots and Flint
1991	Smith Kline and Beecham
1994	Smith Kline Beecham and Pharmacia
1994	Sanofi and Sterling (Pharmacia)
1994	Pharmacia and Erbamont
1994	Hoffmann-La Roche and Pharmacia
1994	American Home Products and Pharmacia
1995	Schwarz Pharma and Rhône-Poulenc
1995	Rhône-Poulenc Rorer and Pharmacia
1995	Pharmacia and Upjohn
1995	Hoechst-Roussel and Mérieux
1995	Gynopharma and Ortho
1995	Glaxo and Burroughs Wellcome
1995	Knoll and Boots
1996	Ciba and Sandoz
1996	SkyePharma and Jago

to provide the fundamental understanding of the granulation process and the rationale behind the selection of the process to further enhance the ability to scale-up the granulation technology transfer, scale-up, and granulation operation, in accordance with the requirements of the industry.

## REFERENCE

1. RH Perry and CH Chilton, *Chemical Engineering*, 8, p. 57, 1973.

ally only as a dryer, and now as a shear mixer can be placed in line. The mixture is granulated in a high shear mixer and transported to the fluid bed dryer to dry. The transfer between them can be controlled. The system optimizes containment, minimized footprint and reduces the footprint required for the process. It is used to produce granulation for tabletting, extruding, spheronizing, and manufacturing of pharmaceutical products. Engineers, and operational managers of the current health care environment in the pharmaceutical industry demand the best containment, demanded by powders that will no longer accept steadily increasing average annual compound rate of price restraint also extends to European payment plans in Germany and other countries. Acquisitions remain the primary product portfolio. The result is an unending series of acquisitions in the pharmaceutical industry. Acquisitions that have taken place since the 1980s or takeover of the significant pharmaceutical companies are the result of research and development. Drug delivery systems for mergers or strategic alliances. The industry is going through, it is becoming a global industry and production must be controlled. The industry sought after are becoming the first. The manufacturing of solid dosage

has taken place in the pharmaceutical industry. This book provides the readers with the information substitute for good science. The chapter with knowledge of granulation technology and the product required will prepare the reader for the industry. Each drug substance is taken into consideration at the process level. Various techniques presented in this book for their understanding and selection of the drug substance. For production in the industry, this book is intended

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1988	Kodak and Sterling
1989	Dow Chemical and Marion Labs
1989	Bristol-Myers and Squibb
1989	American Home Products and A. H. Robins
1990	Pharmacia and Kabi
1990	Boots and Flint
1991	Smith Kline and Beecham
1994	Smith Kline Beecham and Sterling (OTC unit)
1994	Sanofi and Sterling (Prescription unit)
1994	Pharmacia and Erbamont
1994	Hoffmann-La Roche and Syntex
1994	American Home Products and American Cyanamid
1995	Schwarz Pharma and Reed & Carnrick
1995	Rhône-Poulenc Rorer and Fisons
1995	Pharmacia and Upjohn
1995	Hoechst-Roussel and Marion Merrill Dow
1995	Gynopharma and Ortho-McNeil
1995	Glaxo and Burroughs Wellcome
1995	Knoll and Boots
1996	Ciba and Sandoz
1996	SkyePharma and Jago

to provide the fundamental understanding of the technique of granulation, and the rationale behind the selection of each particular technique. This will further enhance the ability to design the production plant, carry out the technology transfer, scale-up, troubleshoot, and maintain the pharmaceutical granulation operation, in accordance with regulatory compliance.

## REFERENCE

1. RH Perry and CH Chilton, Chemical Engineer's Handbook, 5th Edition, Chapter 8, p. 57, 1973.



# 2

## Theory of Granulation

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### I. INTRODUCTION

#### A. Definition of Granulation

Granulation may be considered a size-enlargement process during which small particles are formed into larger, physically strong agglomerates in which the original particles can still be identified. In modern times, granulation technology has been used by a wide range of industries, ranging from

**Table 1** The Advantages and Disadvantages of Wet Granulation

Advantages	Disadvantages
Improved flow properties	Multiple processing steps add complexity and make validation and control difficult
Densification	Time, space, and equipment required are costly
Improved compression characteristics	Stability may be a concern for moisture-sensitive or thermolabile drugs
Better distribution of color and soluble drugs if added in binder solution	Loss of material during various stages of processing
Reduction in dusting	
Prevention of segregation of powder mix	
Makes hydrophobic surfaces more hydrophilic	

the pharmaceutical industry to the fertilizer and minerals-processing industries. Even though pharmaceutical granulations are used primarily to prepare materials for tableting, some granulations are dispensed as such in packets or capsules.

The main objectives of granulation are to improve the flow properties and compression characteristics of the mix, and to prevent segregation of the constituents. However, these gains must be weighed against the fact that granulation requires multiple unit processes, such as wet massing, drying, and screening, which are costly in terms of the time, space, and equipment required, and add complexity because each unit process brings its own set of complications. The advantages and disadvantages of wet granulation are summarized in Table 1.

## B. Types of Granulation

The principal methods of granulating pharmaceuticals may be classified into three main categories: wet processes, dry processes, and other processes. In the wet granulation process, a granulating liquid is used to facilitate the agglomeration process. In the dry granulation process, dry powder particles may be brought together mechanically by compression into slugs or, more frequently today, by roller compaction. Table 2 subdivides each of these

**Table 2** Processes Used for Pharmaceutical Granulation

General process
Wet processes
Dry processes
Other processes

Source: Ref. 1.

categories into specific methods, although some or all these methods may be used in wet granulation has been, a glomeration process. Typically, granulation is carried out in high-shear mixers. Granules are dried in fluidized beds or carried out in fluid bed dryers. Granules are sprayed onto fluidized powder beds to form granules. This latter process is time and space needed for granulation. Other processes are used.

## II. MECHANISMS OF PARTICULATE FORMATION

To understand the mechanisms of granulation, forces giving rise to the cohesion of particles, forces of adhesion and cohesion. *Adhesion* is the force that holds particles together, whereas *cohesion* is the force that holds particles together. Bonds must be formed between particles to form granules, and these bonds must be broken down during the final drying operations. The magnitude of the forces, the structure of the particles, the structure of the liquid, and the tension of the liquid.

Wet Granulation

Disadvantages
processing steps add complexity and make validation and control difficult space, and equipment required are may be a concern for moisture- sensitive or thermolabile drugs material during various stages processing

and minerals-processing indus-  
tries are used primarily to prepare  
granules dispensed as such in packets

to improve the flow properties  
and to prevent segregation of  
granules weighed against the fact that  
processes such as wet massing, drying,  
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of advantages of wet granulation are

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granulation process, dry powder particles  
are compressed into slugs or, more  
commonly, subdivided each of these

Table 2 Processes Used for Pharmaceutical Granulations

General process	Specific methodology
Wet processes	Wet massing Fluid bed granulation Spray drying Pan granulation Extrusion and pelletizing
Dry processes	Roller compaction Slugging
Other processes	Humidification Prilling Melt pelletization

Source: Ref. 1.

categories into specific methods of preparation as given by Record [1]. Although some or all these methods are used in the pharmaceutical industry, wet granulation has been, and continues to be, the most widely used agglomeration process. Typically, the wet massing of pharmaceutical powders is carried out in high-shear mixers before wet screening, and often, the moist granules are dried in fluidized bed equipment. Often, wet granulation is also carried out in fluid bed drier-granulators in which the liquid phase is sprayed onto fluidized powders as the hot airflow simultaneously dries the granules. This latter process requires fewer handling steps and reduces the time and space needed for granulation. Moreover, it can be readily automated. Other processes are used less frequently.

II. MECHANISMS OF PARTICLE BONDING

To understand the mechanism of granulation, it is useful to consider the forces giving rise to the cohesion of moist particles and to the phenomena of adhesion and cohesion. *Adhesion* may be defined as the bonding of unlike materials, whereas *cohesion* is that of like materials. Pharmaceutical dosage forms are heterogeneous and contain powders of varying physical properties. Bonds must be formed between powder particles so that they adhere together to form granules, and these bonds must be sufficiently strong to prevent breakdown of the final dried granules to powder in subsequent handling operations. The magnitude of these forces is determined by the size of the particles, the structure of the granule, the moisture content, and the surface tension of the liquid.

## A. Bonding Mechanisms for Agglomeration

Rumpf [2] identified five mechanisms responsible for the forces operating during and after agglomeration, but stated that usually more than one apply to any particular system. These include the following:

### 1. *Adhesion and Cohesion Forces Caused by the Immobile Liquid Films That Act Like Binder Bridges*

The availability of sufficient moisture to produce a thin, immobile adsorption layer can contribute to the bonding of fine particles by effectively decreasing the distance between particles and increasing the interparticle contact area. This mechanism accounts for the cohesion of slightly moist powders. Residual moisture after drying wet-granulated powders may be present as such thin films, but these are unlikely to contribute significantly to the overall strength of the dried granules. Thin, immobile films of highly viscous bonding media (e.g., solutions of adhesives) can form exceptionally strong bonds, the strength of which can exceed that produced by mobile liquid layers (see Sec. II.A.2).

### 2. *Interfacial Forces and Capillary Pressure at Freely Movable Liquid Surfaces*

When the liquid level on the surface increases beyond that of a thin film, mobile liquid forms bridges wherein capillary pressure and interfacial forces create strong bonds. Although reversible after drying, these bonds precede the formation of solid bridges (see Sec. II.A.3). Mobile liquid films are a prerequisite to the solid bridges formed by binders or other substances dissolved in the granulating fluid.

### 3. *Solid Bridges*

Solid bridges may develop by diffusion of molecules from one particle to another through partial melting at points of contact where high pressures develop, especially at elevated temperatures. This temperature rise can be from an external, secondary source or from friction during agglomeration or energy conversion. Solid bridges can also be built up by chemical reaction, crystallization of dissolved substances, hardening of binders, and solidification of melted components.

### 4. *Attractive Forces Between Solid Particles*

If the particles approach each other closely enough, forces at surfaces can interact to bond particles even in the absence of liquid. These include the

## Theory of Granulation

typical short-range van der Waals type interactions. The former are more important in applications. Because these forces clearly favor this mechanism, in addition, the magnitude of van der Waals forces is much greater than electrostatic forces, and the distance between particles decreases during compaction methods through the application of compaction.

### 5. *Form-Closed Bonds or Bridges*

Fibers, little platelets, or bulk particles, other resulting in "form-closed" bonds. The size of particles influences agglomeration, considered to be small in compaction.

Another method of classification of material bridges between particles is attraction forces.

## B. Bonding Mechanisms

The most widely used process in the industry is wet granulation. The mechanism of wet granulation to be considered that operate during the moistening of liquid bridges that develop between particles. Molecular attractive forces, van der Waals forces, also play an initial role. Interparticle interactions. Van der Waals forces are due to intermolecular attraction forces. Electrostatic forces are generated by the surface which alters surface electron distribution. The attractive forces is to keep particles together. Mechanisms to govern the agglomeration bonding mechanism may be a function of it is difficult to determine if adsorption predominates.

The mechanisms of bonding between particles, interfacial forces between the particles serves to reduce surface impedance by contact by decreasing the effective

## meration

responsible for the forces operating and that usually more than one apply the following:

### *Caused by the Immobile Bridges*

produce a thin, immobile adsorption particles by effectively decreasing the interparticle contact area. on of slightly moist powders. Reduced powders may be present as such contribute significantly to the overall immobile films of highly viscous bond- in form exceptionally strong bonds, reduced by mobile liquid layers (see

### *Pressure at Freely*

increases beyond that of a thin film, capillary pressure and interfacial forces after drying, these bonds precede (II.A.3). Mobile liquid films are a by binders or other substances dis-

of molecules from one particle to s of contact where high pressures ures. This temperature rise can be m friction during agglomeration or o be built up by chemical reaction, hardening of binders, and solidifi-

### *Particles*

ely enough, forces at surfaces can sence of liquid. These include the

typical short-range van der Waals forces, electrostatic forces, or magnetic-type interactions. The former two are of greater relevance to pharmaceutical applications. Because these are surface forces, decreasing particle size clearly favors this mechanism by increasing the surface/mass ratio. In addition, the magnitude of van der Waals forces, which are severalfold stronger than electrostatic forces, can be expected to increase substantially as the distance between particles decreases, and this is achieved in dry granulation methods through the application of pressure, as in slugging or roller compaction.

### *5. Form-Closed Bonds or Interlocking Bonds*

Fibers, little platelets, or bulky particles can interlock or fold about each other resulting in "form-closed" bonds. Although mechanical interlocking of particles influences agglomerate strength, its contribution is generally considered to be small in comparison with other mechanisms.

Another method of classification distinguishes between the presence of material bridges between the primary particles in the agglomerates and attraction forces.

## **B. Bonding Mechanisms in Wet Massing**

The most widely used process of agglomeration in the pharmaceutical industry is wet granulation. Therefore, it is important to understand the mechanism of wet granulation to better control the process. The cohesive forces that operate during the moist agglomeration process are mainly due to the liquid bridges that develop between the solid particles, even though intermolecular attractive forces, van der Waals forces, and electrostatic forces also play an initial role. Intermolecular attractive forces are short-range interactions. Van der Waals forces, in general, make the largest contribution to intermolecular attraction owing to a longer range of effectiveness [3]. Electrostatic forces are generated primarily through interparticle friction, which alters surface electron states. The overall contribution of electrostatic attractive forces is to keep particles in contact long enough for other mechanisms to govern the agglomeration process [2]. In practice, more than one bonding mechanism may be acting simultaneously. With very fine powders, it is difficult to determine if bonding through long-range forces or through adsorption predominates.

The mechanisms of bonding in the wet state depend on capillary and interfacial forces between the particles. Immobile, adsorbed surface liquid serves to reduce surface imperfections and increases particle-particle contact by decreasing the effective interparticle distance. Once sufficient liquid



immobile surface liquid state to a way-Jones [4] defined this theory Barlow [5] added a fourth. These, capillary, and droplet or suspension in Fig. 1. The mechanism of change from a triphasic stage is in pendular and funicular state assembly, in which the granulates.

progressive increase in the moisture capillary forces until the droplet by surface tension holds the droplet at interfacial forces. At low moisture, shaped rings at the points of contact *pendular state* (see Fig. 1a). Here, tension at the solid-liquid-air interface of the liquid bridge. As the mois-

ture content increases, the rings coalesce to form a continuous network of liquid interspersed with air. This state is called the *funicular state* (see Fig. 1b). With a further increase in water content the *capillary state* (see Fig. 1c) is reached when all the pore spaces in the granule are completely filled with liquid, and concave menisci develop at the surface of the agglomerate. The *droplet state* (see Fig. 1d) occurs when the liquid completely surrounds the granule, resulting in an external phase consisting of liquid, with an internal solid phase [5]. The strength of the droplet is dependent on the surface tension of the liquid phase.

A granule initially consists of moist particles that have partly coalesced to form loose aggregates held together by pendular bonds. The kneading action of the granulator brings the particles closer together so that the internal pore space in the aggregates is reduced and, if the moisture content is sufficient, the pores eventually become saturated. From geometric considerations of smooth spheres in close proximity, Flemmer [6] reported the levels of moisture content (%MC by volume) for the three stages of granule growth:

Pendular regimen:  $0 < \%MC < 13.6$

Funicular regimen:  $13.6 < \%MC < 100$

Capillary regimen:  $\%MC = 100$

The characteristics of the granules from various stages of the granulation are given Table 3.

The basic wet-granulated unit may be visualized as two particles and a liquid bridge that serves to hold the particles together by surface tension at the air-liquid interface and by hydrostatic suction. Most mixers apply varying degrees of shear to the wet mass. Shear forces applied cause differential particle movement and can break the liquid bridge. It is often considered that most wet granulation processes are a balance between agglomerative growth and breakdown. To initiate granulation, there must be nuclei

**Table 3** Characteristics of the Granules from Different Stages of Granulation

Aggregate type	Characteristics
Pendular	Typically nonspherical, "dry" surface, soft, low density
Funicular	More nearly spherical, "dry" surface, firm, denser than pendular
Capillary	Tend to be spherical, surface normally wet, dense, plastic
Kneaded capillary	Maximal density and consistency

erate during wet granulation: (a) pendular, (b) funicular, (c) capillary, (d) droplet state.

at which primary particles collect around a drop of the granulating fluid. Nucleation is followed by consolidation caused by liquid surface tension. The growth of granules can also proceed by coalescence between colliding agglomerates. Granules so formed may be considered to be approximately saturated and to have a slight excess of moisture at their surface. This allows a certain degree of "surface plasticity," which enables partial deformation to occur when two granules are in collision, and the excess moisture available effects coalescence across the larger area of contact so produced by the deformation. On the other hand, a granule containing less moisture is more rigid and, with no excess moisture on the surface, would not, on collision with another granule, be able to coalesce. Such "surface dry" granules, however, might be able to hold smaller individual particles if the latter were sufficiently moist to form a "pendular bond" at the point of contact. A granule with high moisture content can coalesce with a smaller granule.

Layers of viscous fluids may be formed in the same manner as the mobile liquid bridges. However, owing to the high viscosity and associated adhesive properties of such fluids, these bonds are considered to be immobile, but are treated in a manner similar to that of the mobile bridges.

Usually, the moist agglomerate is only a transition state for the final product. With drying, the liquid is driven off and solid bridges will form by crystallization or hardening of binder, resulting in a significantly stronger agglomerate. Solid bond formation can also occur in a situation when particle melting or localized fusion welding—particle deformation, followed by sintering and chemical reaction—takes place. Particle melting or localized fusion welding may occur at point contacts where melting of asperities under pressure leads to the formation of a liquid that resolidifies to form solid bonds. Sintering describes the bonding of adjacent surfaces that may be due to viscous or plastic flow, evaporation, and condensation or diffusion.

Warren and Price [7], while studying liquid migration effects, noted that greater migration occurred with smaller component particles in the agglomerate as a result of greater suction pressure and increased intragranular contact area. The greater the surface area, the greater are such effects during wet massing, and this is reflected in greater wet tensile strength of the mass. Practically, it may be observed during wet massing that, for a given liquid content, the tensile strength, bulk density, and apparent moisture content increase as mixing progresses. As massing continues, tensile strength eventually reaches a maximum and then declines, probably owing to a lubricant effect of the liquid content; the mass may then be described as a paste. These changes result from the capillary forces, which tend to draw particles closer together, and the gradual removal of air from the mix under the combined effect of shear and compression forces in the massing equipment.

### III. GRANULE GROWTH

The mechanism of particle growth in a balling drum to granulate narrow-range powders has been studied by Sastry et al. [8] who studied the mechanism of granule growth in a balling drum. The

1. *Nucleation*: Nucleation occurs when particles come in contact each other and form a nucleus.
2. *Transition*: Nuclei formed by the collision of two or more nucleated particles can be reshaped by the agglomeration of particles by the presence of liquid. If the nuclei are of wide size distribution, the larger, this point represents the transition in capsule and tablet formation.
3. *Ball growth*: Further growth of granules, and the rate of growth increases with time. The growth will continue and the granule size will increase though this is ultimately limited by the properties of the powder.

Sastry and Fuerstenau [9] studied the mechanism of granule growth and summarized four principal mechanisms:

1. *Layering*: The powder particles adhere to existing granules and increase granule size.
2. *Crushing and layering*: The powder particles adhere to other granules and form a new granule.
3. *Coalescence*: Two granules coalesce to form a larger granule.
4. *Abrasion transfer*: A granule adheres to other granules and transfers its mass to them.

There is always some degree of difficulty in identifying a given



a drop of the granulating fluid. caused by liquid surface tension. y coalescence between colliding considered to be approximately moisture at their surface. This city," which enables partial de- re in collision, and the excess oss the larger area of contact so r hand, a granule containing less s moisture on the surface, would able to coalesce. Such "surface hold smaller individual particles a "pendular bond" at the point e content can coalesce with a

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ly a transition state for the final ff and solid bridges will form by ulting in a significantly stronger o occur in a situation when par- —particle deformation, followed place. Particle melting or local- tacts where melting of asperities a liquid that resolidifies to form ng of adjacent surfaces that may on, and condensation or diffusion. g liquid migration effects, noted er component particles in the ag- ssure and increased intragranular he greater are such effects during wet tensile strength of the mass. massing that, for a given liquid , and apparent moisture content continues, tensile strength even- es, probably owing to a lubricant y then be described as a paste. ces, which tend to draw particles air from the mix under the com- es in the massing equipment.

### III. GRANULE GROWTH MECHANISMS

The mechanism of particle growth has been investigated using a rotating drum to granulate narrow- and wide-particle-sized feed material. Kapur et al. [8] studied the mechanisms of granulation by agglomerating limestone powder in a balling drum. They divided granulation into three stages:

1. *Nucleation*: Nucleation is the start of granulation as particles contact each other and adhere owing to liquid bridges.
2. *Transition*: Nuclei grow by two possible mechanisms: Either single particles can be added to the nuclei by pendular bridges, or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. If the size distribution is not excessively large, this point represents a suitable endpoint for granules used in capsule and tablet manufacture.
3. *Ball growth*: Further granule growth results in large, spherical granules, and the mean particle size of the granulating system increases with time. If agitation is continued, granule coalescence will continue and produce an unusable, overmassed system, although this is ultimately dependent on the amount of liquid added and the properties of the material being granulated.

Sastry and Fuerstenau [9] studied particle growth during agglomeration and summarized four principal mechanisms as illustrated in Fig. 2:

1. *Layering*: The powder mix that is added to the granulation adheres to existing granules forming a surface layer and increasing the granule size.
2. *Crushing and layering*: Some granules break into fragments that adhere to other granules forming a layer of material over the surviving granule.
3. *Coalescence*: Two or more granules join to form a larger granule.
4. *Abrasion transfer*: Abraded material caused by attrition of granules adheres to other granules, thereby increasing their size.

There is always some degree of overlap between these stages, and it is very difficult to identify a given stage by inspection of the granulating system.

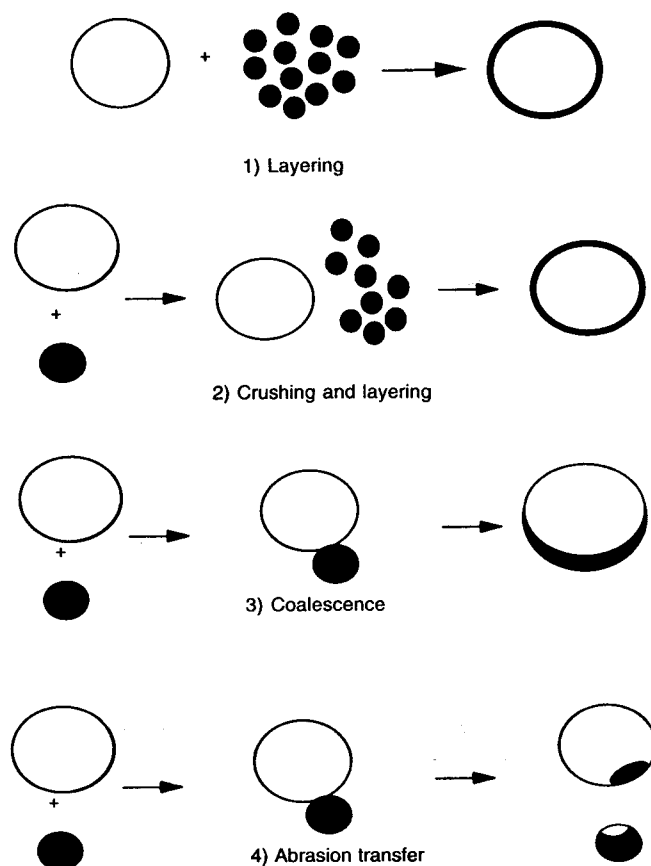


Fig. 2 Schematic representation of various mechanisms of the granulation.

#### IV. MODELS DESCRIBING THE STRENGTH OF AGGLOMERATES

The relative strength of the bonds that form during granulation by agitation affect both the mechanism and kinetics of granule growth and such final product properties as friability, dissolution rate, and density. The forces contributing to the formation of agglomerates, or those holding the particles together in an agglomerate, can be divided into three categories. They are forces caused by the liquid distributed between the particles (mobile liquid in various stages, such as pendular, funicular, and capillary); bonding ma-

#### Theory of Granulation

terial between the particles (bonds). The forces holding the particles together (bonds) depend on the forces holding the particles together (bonds). If more than one type of force is involved, it is often difficult to attribute the strength of the bond to any one type of force.

To gain a better understanding of the granulation process, researchers have developed theoretical models. Because of the complexity of the process, several assumptions are usually made. One of the most common is a particle assembly in which the forces are estimated by Rumpf [2] from the following assumptions:

1. The particles may be considered as spheres that are perfectly spherical.
2. There are a large number of particles.
3. The bonds are statistical in nature.
4. The interparticle bonds are equivalent to the mean tensile strength of the material.

Thus, the major parameters of an agglomerate with localized bonds are:

$$TS = \frac{9}{8} \frac{1 - \epsilon}{\pi d^2} kH$$

in which

$TS$  = mean tensile strength  
 $d$  = diameter of the sphere  
 $\epsilon$  = the porosity of the agglomerate

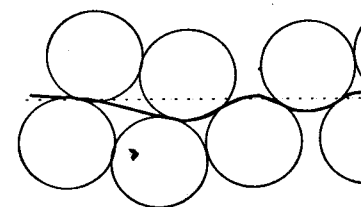
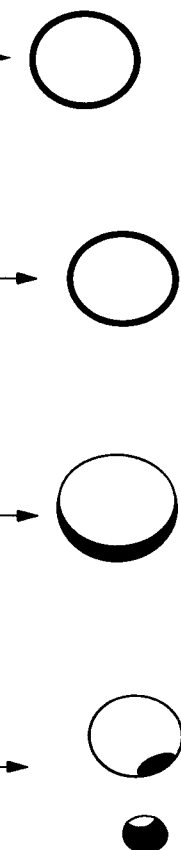


Fig. 3 Schematic representation of a granule structure. The dashed line represents ideal fracture and the solid line represents the actual fracture.



s mechanisms of the granulation.

## TRENGTH

form during granulation by agitation  
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between the particles (mobile liquid  
icular, and capillary); bonding ma-

terial between the particles (both localized and interparticle); and van der Waals, electrostatic, and magnetic forces. The strength of an agglomerate depends on the forces holding the agglomerate together, and there is often more than one type of force that is responsible for the agglomerate strength; therefore, it is often difficult to calculate the strength of agglomerates based on any one type of force.

To gain a better understanding of the granulation process, researchers have developed theoretical models to describe the strength of the agglomerates. Because of the complexity of the granulation process, simplifying assumptions are usually made. For example, the mean tensile strength of a particle assembly in which bonds are localized at point contacts was estimated by Rumpf [2] from a model based on Fig. 3 and the following assumptions:

1. The particles may be represented by a large number of monodisperse spheres that are distributed statistically in the agglomerate.
2. There are a large number of bonds in the stressed cross section.
3. The bonds are statistically distributed over the fracture section.
4. The interparticle bond strength between individual particles is equivalent to the mean value of the entire agglomerate.

Thus, the major parameters that determine the tensile strength of an agglomerate with localized bonding were identified by Rumpf in Eq. (1) [2].

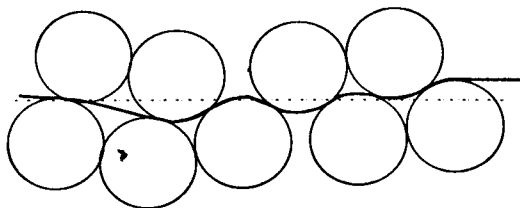
$$TS = \frac{9}{8} \frac{1 - \epsilon}{\pi d^2} kH \quad (1)$$

in which

$TS$  = mean tensile strength per unit cross section area

$d$  = diameter of the spherical particles

$\epsilon$  = the porosity of the assembly



**Fig. 3** Schematic representation of the fracture area through an agglomerate: dotted line represents ideal fracture and solid line represents real fracture. (From Ref. 2.)

$k$  = the mean number of points of contact between a spherical particle and its neighbors (i.e., a coordination number, which is a function of void fraction and the packing arrangement).

$H$  = tensile strength of a single bond or the binding forces between the particles.

The application of Eq. (1) requires knowledge of the tensile strength of a single bond and of  $\epsilon$ ,  $d$ , and  $k$ . The porosity  $\epsilon$  is obtained from the apparent or bulk density of the packing  $\rho_b$  and the solid particle density  $\rho_s$ :

$$\epsilon = 1 - \frac{\rho_b}{\rho_s} \quad (2)$$

The coordination parameter  $k$  is difficult to estimate. Rumpf [2] has approximated this value by correlation with porosity through the expression  $k\epsilon \approx \pi$ . When this value is substituted into Eq. (1), the mean tensile strength can be represented by Eq. (3):

$$TS \cong \frac{9}{8} \frac{1 - \epsilon}{\epsilon} \frac{H}{d^2} \quad (3)$$

### A. Mobile Liquid Bridges

The types of low-viscosity liquid bonds in an agglomerate are shown in Fig. 1. The attractive forces in such systems originate with the interfacial tension at the liquid surface and the pressure deficiency (suction) created within the liquid phase by curvature at the liquid surface; they have been calculated [2,4] for spherical packing systems.

When liquid levels are low, lens-shaped liquid rings are formed at points of contact (pendular state), and bonding is localized at points of contact. These liquid rings begin to coalesce as the moisture level increases. The pore volume occupied by liquid at which this transition from the pendular state begins to occur may be calculated for monodisperse spheres and is about 18%, assuming cubic packing, and about 24%, assuming rhombohedral packing.

For two smooth, spherical particles in a pendular state, as shown in Fig. 4, the tensile strength may be estimated from Eq. (4) [4], with the assumption that the liquid completely wets the surface of the particles (i.e., contact angle = 0):

$$H = \gamma d \left[ \frac{\pi}{1 + \tan(\phi/2)} \right] = \gamma d F(\phi) \quad (4)$$

where  $\gamma$  is the surface tension of the liquid,  $d$  is the particle diameter,  $\phi$  is

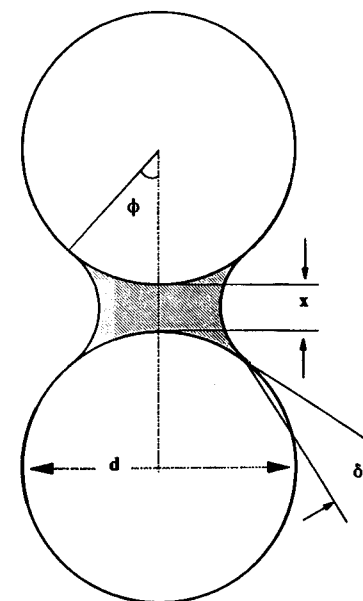


Fig. 4 Schematic diagram of two spherical particles in a pendular state in the calculation of cohesive force (from Ref. 12.)

the semiangle of the liquid ring ( $\phi$ ,  $\delta$ ). The calculated value of  $H$  is substituted into Eq. (3) to yield the mean tensile strength of the agglomerate in the pendular state. Theoretically, as the moisture level increases, the tensile strength between the particles increases due to the increased curvature to the liquid surface and the pressure deficiency within the liquid. For a given moisture level, the percentage saturation  $S$ . Curve 1 shows the tensile strength of an agglomerate as a function of the value increasing with reduced moisture level. Rumpf and Carr [11] found the tensile strength to increase or to diminish with decreasing moisture level. In practice, no absolutely smooth transition is observed. This discrepancy to the separation distance  $x$  as shown in Fig. 4.

$$H = \gamma d F \left( \phi, \frac{x}{d} \right)$$

contact between a spherical particle  
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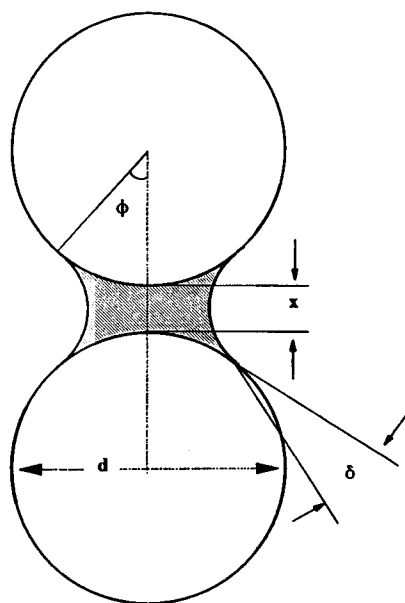
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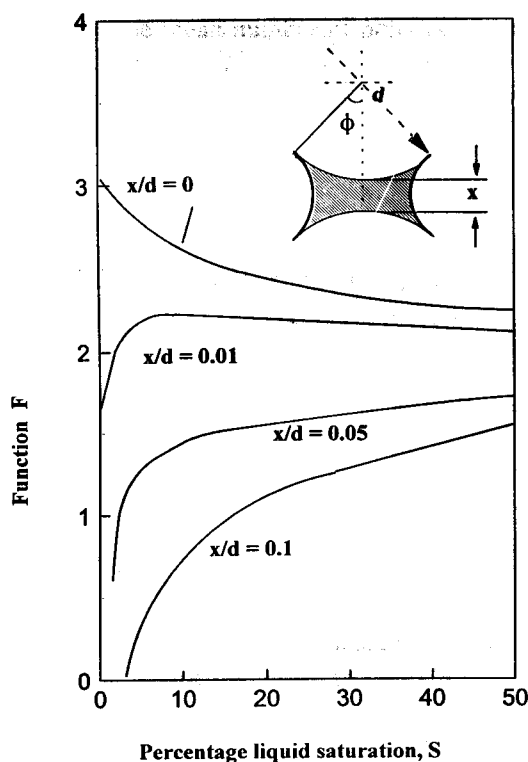
iquid,  $d$  is the particle diameter,  $\phi$  is



**Fig. 4** Schematic diagram of two spheres in pendular bond: The symbols are used in the calculation of cohesive force between the two spherical particles. (Redrawn from Ref. 12.)

the semiangle of the liquid ring between the two spheres, and  $F$  is a function of  $(\phi, \delta)$ . The calculated values of  $H$  may be substituted directly into Eq. (3) to yield the mean tensile strength of the agglomerate in the pendular state. Theoretically, as the moisture content in the pendular state is removed, the tensile strength between the two particles would increase owing to the increased curvature to the liquid surface, resulting in a very high pressure deficiency within the liquid. Figure 5 shows a plot of function  $F$  against the percentage saturation  $S$ . Curve 1 ( $x/d = 0$ ) is a theoretical profile for the tensile strength of an agglomerate of two smooth spherical particles showing the value increasing with reduction of the moisture. However, Pietsch [10] and Carr [11] found the tensile strength to be either approximately constant or to diminish with decreasing moisture content in this state. Because, in practice, no absolutely smooth particles are found, Pietsch [12] attributed this discrepancy to the separation caused by asperities in real particles, and introduce a separation  $x$  as shown in Fig. 4 and in Eq. (4), as follows:

$$H = \gamma d F \left( \phi, \frac{x}{d} \right) \quad (5)$$



**Fig. 5**  $F(\phi)$  in Eq. (7) and  $F(\phi, x/d)$  in Eq. (8) as a function of liquid saturation,  $S$ , porosity;  $\epsilon = 0.35$ . (From Ref. 2.)

where  $F(\phi, x/d)$  is a function of  $\phi$  and  $x/d$ , and the approximate values are shown in Fig. 5 for zero contact angle. It can be seen from Fig. 5 that for constant  $\gamma$  and  $d$ , the tensile strength remains constant or decreases with decreasing moisture content as  $x/d$  increases. Pietsch [13] suggested that a value of 2 may be assigned to  $F(\phi, x/d)$  throughout this region. Use of this value in Eq. (5) and substituting that value of  $H$  in Eq. (3) results in the tensile strength of a pendular agglomeration in which the binding liquid completely wets the particles.

$$TS = \frac{9}{4} \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d} \quad (6)$$

When the liquid content of an assembly exceeds that required to support a pendular assembly, the funicular state (see Fig. 1b) is reached in which

the particles are held together with air. When all pores are reached (see Fig. 1c). In the pendular state, the tensile strength depends on the pressure deficiency in the capillary state and the pressure deficiency using the Laplace equation

$$P = \frac{2\gamma}{r} \cos \delta$$

where  $P$  is the pressure deficiency in the capillary state,  $r$  is the mean hydraulic radius, and  $\delta$  is the contact angle.

For monodisperse spherical particles, the mean hydraulic radius based on the porosity, resulting in the following equation

$$TS \cong P_e \cong 6 \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d} \cos \delta$$

where  $P_e$  is the maximum pressure deficiency in the capillary state. If the particles are irregular in shape, Eq. (8) can be modified as follows

$$P_e = TS = K \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d}$$

where  $K$  is a constant that is a function of particle shape and accounts for the nonspherical shape of the particles. For irregular particles of reasonable shape,  $K$  varies between 1 and 2. In the pendular state, the tensile strength of an agglomeration is about one-third that of the capillary state. The partial saturation of the void space may be estimated from

$$TS = sK \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d}$$

where  $s$  is the fractional saturation of the void space for moisture contents close to the pendular state.

When the capillary state is reached, the particles are completely enveloped by the liquid. The particles tend to be held in droplets by the surface tension of the continuous liquid drop



the particles are held together by a continuous network of liquid interspersed with air. When all pores become filled with liquid, the capillary state is reached (see Fig. 1c). In the capillary state, the tensile strength largely depends on the pressure deficiency in the liquid, rather than on the interfacial tension at the assembly surface. Thus, the tensile strength of an agglomerate in the capillary state can be reasonably estimated from this pressure deficiency using the Laplace equation for a circular capillary:

$$P = \frac{2\gamma}{r} \cos\delta \quad (7)$$

where  $P$  is the pressure deficiency,  $r$  is the radius of the capillary, and  $\delta$  is the contact angle.

For monodisperse spheres, the capillary radius may be replaced with the mean hydraulic radius based on the specific surface of the particles and the porosity, resulting in the following equation

$$TS \cong P_e \cong 6 \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d} \cos\delta \quad (8)$$

where  $P_e$  is the maximum suction pressure, and  $\epsilon$  is the porosity. If the particles are irregular in shape and the liquid completely wets the solid, Eq. (8) can be modified as follows:

$$P_e = TS = K \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d} \quad (9)$$

where  $K$  is a constant that is related to the specific surface of the powder and accounts for the nonspherical shape of the particles. The value of  $K$  for irregular particles of reasonably uniform dimensions [4] may be taken as 4 and, for sand particles,  $K$  varies from 6 to 8. The tensile strength in the pendular state is about one-third that in the capillary state, and the tensile strength of agglomerate in the funicular state takes a value intermediate between that of the capillary and pendular states. By accounting for the partial saturation of the void spaces, the tensile strength of the funicular state may be estimated from

$$TS = sK \frac{1 - \epsilon}{\epsilon} \frac{\gamma}{d} \quad (10)$$

where  $s$  is the fractional saturation of the voids. This equation holds best for moisture contents close to the capillary state.

When the capillary state is exceeded, liquid content is sufficient to completely envelope the particles (see Fig. 1d). In this case, the particles tend to be held in droplets by the interfacial tension of the convex surface of the continuous liquid droplet surface.

Eq. (8) as a function of liquid saturation,

$x/d$ , and the approximate values are  
It can be seen from Fig. 5 that for  
remains constant or decreases with  
eases. Pietsch [13] suggested that a  
) throughout this region. Use of this  
value of  $H$  in Eq. (3) results in the  
variation in which the binding liquid

(6)

assembly exceeds that required to sup-  
state (see Fig. 1b) is reached in which

## B. Interparticle Bonding

For many of the interparticle adhesive mechanisms, the value of  $H$  in Eq. (3) cannot be calculated from theory. Generally, the stronger types of bonding (e.g., solid bridging and high-viscosity liquid bonding) can be modeled theoretically only in the simplest cases, with the following assumptions:

1. That a solid bridging material is distributed over all interparticle contacts uniformly
2. That they have constant tensile strength
3. That failure occurs only through these bridges

The tensile strength of the assembly may be estimated from the following equation:

$$TS = \frac{W_B}{W_P} \frac{\rho_P}{\rho_B} (1 - \epsilon) \sigma_B \quad (11)$$

where  $W_B/W_P$  represents the ratio by weight of binding material to particles,  $\rho_P$  and  $\rho_B$  are, respectively, the densities of the particles and bonding material,  $\epsilon$  is the porosity of the mass, and  $\sigma_B$  is the tensile strength of the binding material.

The strength of a bond depends on (a) the cohesive strength of a given particle, (b) the interfacial bond strength of the material bonding to this particle, (c) the cohesive strength of the bonding material, (d) the interfacial bond strength to a second particle, (e) and the cohesive strength of the second particle. The interactions that lead to bonding between particles is a very complex phenomenon. Blomquist [14] likened an adhesive-bonded joint to a chain of at least five links. The strength of the bond is the strength of the weakest of the links. Unfortunately, the total strength of the bridge cannot be adequately estimated from theoretical estimates of the primary short-range and secondary long-range bonds involved in this chain [14] because they do not account for other effects that affect the strength of the interaction, such as residual stresses at the interface, elastic effects, and the presence of any surface impurities.

When interparticle-bonding material is not present, relatively weak secondary (long-range) forces may contribute substantially to agglomeration if the particles are finely divided and in intimate contact. These were theoretically and experimentally investigated by Krupp [15] and Rumpf [2]. For example, Rumpf [2] employed the following equation to estimate the van der Waals interaction between two quartz spheres:

$$H = 4.2 \times 10^{-14} \frac{d}{x^2} \left( \frac{\text{dynes}}{\text{cm}^2} \right) \quad (12)$$

where  $d$  is the diameter (cm) (cm) between them. Thus, a  $\mu\text{m}$  with distance between porosity of 0.40, will have a In general, the contributions (especially) to the strength of van der Waals forces [2].

The mechanisms of bonding though models for these processes, they nevertheless provide involved in granulation.

## REFERENCES

1. PC Record. A review of Technol Prod Manuf 1:32.
2. H Rumpf. The strength of Agglomeration. New York
3. PJ Sherrington, R Oliver.
4. DM Newitt, JM Conway. granulation. Trans Inst Ch
5. CG Barlow. Granulation c 1968.
6. CL Flemmer. On the reg Powder Technol 66:191-1
7. JW Warren Jr, JC Price. J
8. PC Kapur, DW Fuerstenau 348-355, 1964.
9. KVS Sastry, DW Fuerste pelletization. Powder Tech
10. W Pietsch, E Hoffman, H Eng Chem Prod Res Dev
11. JF Carr. Tensile strength c
12. W Pietsch. Tensile strengt
13. W Pietsch. Adhesion and handling—a survey. J Eng
14. RF Bloomquist. Adhesive: nology, Vol. 1. 2nd ed. Ne
15. H Krupp. Particle adhesio



mechanisms, the value of  $H$  in Eq. (1) is generally, the stronger types of bonding (e.g., liquid bonding) can be modeled with the following assumptions:

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(11)

weight of binding material to particles,  $\rho_p$  is the density of the particles and bonding material,  $\sigma_p$  and  $\sigma_B$  is the tensile strength of the particles and bonding material, respectively.

(a) the cohesive strength of a given material, (b) the strength of the material bonding to this bonding material, (d) the interfacial strength and the cohesive strength of the material, and (e) the strength of the bond to bonding between particles is a function of the strength of the bond. [14] likened an adhesive-bonded material to a chain of particles. The strength of the bond is the strength of the chain. The total strength of the bridge is the sum of the strengths of the individual bonds. Theoretical estimates of the primary factors involved in this chain [14] include the strength of the bond, the strength of the interface, elastic effects, and the strength of the material.

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where  $d$  is the diameter (cm) of the spherical particles and  $x$  is the distance (cm) between them. Thus, an agglomerate of particles with a diameter of 1  $\mu\text{m}$  with distance between the particles at 25  $\text{\AA}$  and having a moderate porosity of 0.40, will have a theoretical tensile strength of about 10  $\text{g/cm}^2$ . In general, the contributions of magnetic interactions or electrostatic forces (especially) to the strength of agglomerates are small in comparison with van der Waals forces [2].

The mechanisms of bonding and granule formation are complex. Although models for these processes require numerous simplifying assumptions, they nevertheless provide useful insight into the physical phenomena involved in granulation.

## REFERENCES

1. PC Record. A review of pharmaceutical granulation technology. *Int J Pharm Technol Prod Manuf* 1:32–39, 1988.
2. H Rumpf. The strength of granules and agglomerates. In: WA Knepper, ed. *Agglomeration*. New York: Wiley-Interscience, 1962, pp. 379–418.
3. PJ Sherrington, R Oliver. *Granulation*. London: Heyden & Son, 1981.
4. DM Newitt, JM Conway-Jones. A contribution to the theory and practice of granulation. *Trans Inst Chem Eng (Lond)* 36:422–442, 1958.
5. CG Barlow. Granulation of powders. *Chem Eng (Lond)* 220:CE196–CE201, 1968.
6. CL Flemmer. On the regime boundaries of moisture in granular materials. *Powder Technol* 66:191–194, 1991.
7. JW Warren Jr, JC Price. *J Pharm Sci* 66:1406–1409, 1977.
8. PC Kapur, DW Fuerstenau. Kinetics of green pelletization. *Trans AIME* 229:348–355, 1964.
9. KVS Sastry, DW Fuerstenau. Mechanisms of agglomerate growth in green pelletization. *Powder Technol* 7:97–105, 1973.
10. W Pietsch, E Hoffman, H Rumpf. Tensile strength of moist agglomerates. *Ind Eng Chem Prod Res Dev* 8:58–62, 1969.
11. JF Carr. Tensile strength of granular materials. *Nature* 213:1158–1159, 1967.
12. W Pietsch. Tensile strength of granular materials. *Nature* 217:736–737, 1968.
13. W Pietsch. Adhesion and agglomeration of solids during storage, flow and handling—a survey. *J Eng Ind* 91 (Ser. B):435–449, 1969.
14. RF Bloomquist. Adhesives. In: Kirk-Othmer *Encyclopedia of Chemical Technology*, Vol. 1. 2nd ed. New York: Interscience, 1963, pp. 371–405.
15. H Krupp. Particle adhesion. *Adv Colloid Interfacial Sci* 1:111–239, 1967.

# 3

## Drug Substance and Excipient Characterization

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## I. INTRODUCTION

Characterization of drug substances and excipients is a very important step at the preformulation phase of product development. Although testing will involve additional time and cost, failure to carry out the appropriate characterization tests can be even more costly to manufacturers if the products made are not within specifications. Preformulation characterization of raw materials creates a body of information that is very useful in the development of products. The lack of such information leaves the formulator with little leeway for remediation action when a problem arises from the production process or from the quality of the finished product. It is important to eliminate the possible influences of the raw material characteristics before venturing into investigation of processing variables. The knowledge derived from the characterization of raw materials can also serve to enable better specifications to be drawn up for procuring materials, with the aim of either reducing cost or improving a product's quality. In addition, a review of material characterization results can provide an excellent database for the assessment of suppliers who can provide materials of consistent quality.

Materials from reputable companies may be supplied with detailed specifications, and their methods of determination may be obtained, if requested. The information on specifications, such as purity or content, is very often available. Nevertheless, it is prudent to confirm such information. The information provided by different suppliers may vary. The type of tests carried out or the techniques used for the characterization of a particular physical property, for example, the particle size distribution, may be different. Comparison of materials from different suppliers, therefore, can be difficult. Sometimes, the analytical result supplied by the manufacturer is given as falling within a certain range, and this gives virtually no information about batch-to-batch variation of the material.

Consequently, it is important to have a system for in-house characterization of raw materials alongside the stability and functional tests for the finished product. Whenever possible, tests carried out should yield quantitative results, rather than a pass-fail or present-absent assessment. Retro-

spective studies of the finished product, documented production processes, and raw materials, can provide the direction for improvement and can improve the specific characteristics of the product.

The method of material characterization depends on the nature and form of the material involved in the conversion of raw materials into a desirable characterization test. The choice of test and the likely use or influence of the test on the process or product. For instance, the effect of the distribution of a drug material on its solubility in a solution, more important when the material is critical when preparing an injectable solution, translated into additional costs. The number of tests to be carried out on a material, the usefulness of tests to give a clear picture of materials, their effects during processing, and the rationality and aesthetics of the final product.

The task of building up a system for material characterization is difficult, given the wide spectrum of materials and pharmaceutical granulation. Many companies have aspects of testing and rarely have a comprehensive set of excipient materials. The physical and chemical properties of their chemical properties to ensure consistency of process as well as the quality of the final product. The ability to define excipients and their effects on the product undoubtedly benefit the formulation process. The help eliminate many process problems. The characterization tests, such as particle size distribution, are important, but discussion of the results should be done separately.

## II. PARTICLE SHAPE, SIZE, AND DISTRIBUTION

### A. Particle Shape

Particle shape is an important factor in determining the bulk properties of a powder. A powder with a high surface area and have a lower surface/volume ratio. The importance of particle shape, the more irregular the shape, the more defined owing to the complex nature of the particles. In general, shape mea-

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excipients is a very important step in product development. Although testing will be required to carry out the appropriate characterization to manufacturers if the products are to be used in the development of a new formulation, characterization of raw materials is very useful in the development of a new product. Formulation leaves the formulator with a problem arises from the production of a finished product. It is important to know the raw material characteristics before they are used in the formulation. The knowledge derived from these tests can also serve to enable better selection of raw materials, with the aim of either improving quality. In addition, a review of the literature can provide an excellent database for the selection of materials of consistent quality.

Excipients may be supplied with detailed information. Determination may be obtained, if required, such as purity or content, is very important to confirm such information. The type of tests carried out may vary. The type of tests carried out for characterization of a particular physical property, such as particle size distribution, may be different. Suppliers, therefore, can be difficult to choose. Information by the manufacturer is given as a guide, but it provides virtually no information about the product.

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spective studies of the finished product's test results, together with well-documented production process validation and characterization tests of raw materials, can provide the direction for refinement of the production process and can improve the specifications for raw materials.

The method of material characterization varies considerably, for it depends on the nature and form of material used as well as the process involved in the conversion of the raw materials to the finished products. The desirable characterization test for each material depends on the material itself and the likely use or influence of a particular material property on the process or product. For instance, detailed information of the particle size distribution of a drug material may be less important when the end product is a solution, more important when the material is to be granulated, and most critical when preparing an inhalant. Because unnecessary testing can be translated into additional cost, careful consideration of the type and number of tests to be carried out on the raw materials should be weighed against the usefulness of tests to give information on the identity and quality of raw materials, their effects during processing and manufacturing, and the functionality and aesthetics of the finished products.

The task of building up a body of information on materials is indeed difficult, given the wide spectrum of drugs and excipients used in pharmaceutical granulation. Many compendial tests are concerned with the chemical aspects of testing and rarely address the physical characterization of excipient materials. The physical aspects of raw materials are more likely than their chemical properties to exert a greater influence on the granulation process as well as the quality and functionality of the finished products. The ability to define excipients using the correct functionality tests would undoubtedly benefit the formulator greatly, for better defined excipients could help eliminate many processing problems. It is obvious that some material characterization tests, such as determination of identity and purity, are important, but discussion of them is not included because they are better dealt separately.

## II. PARTICLE SHAPE, SIZE, AND SURFACE AREA

### A. Particle Shape

Particle shape is an important parameter that can have a significant effect on the bulk properties of a powder; spherical particles flow better, pack better, and have a lower surface/volume ratio. Despite the well-recognized importance of particle shape, the method of shape determination has not been clearly defined owing to the complexity and variability of the three-dimensional particles. In general, shape measurement methods are able to accurately define

the shape only if the shape of constituent particles can be correctly predicted based on a two-dimensional model.

The shape of particles may be assessed descriptively by terms such as spherical, elongated, acicular, angular, or a host of other terms. Although these are descriptive terms, if accurately used, they can convey a general idea of the particle shape. However, they reveal little about the degree to which the particles take on a particular shape. Without a comparable quantitative measure, it may be difficult to assess the effects of particle shape on a process or product.

From the linear dimensional description of breadth, length, and height, some shape data can be derived. *Breadth* is usually defined as the minimum distance between two parallel lines bracketing the particle, whereas *length* is the maximum distance between two parallel lines enclosing the particle and is perpendicular to the breadth. The *height* is the thickness of the particle resting in its most stable orientation. The measurement of height is generally difficult for small particles because they are usually viewed through a microscope.

Direct microscopic measurement of particle dimensions is very tedious. The particle dimension is obtained using a linear eyepiece graticule. A camera lucida attachment may be used to trace out the outline of particles onto a paper. The perimeter of particle tracing may be obtained by either using a string or a planimeter. The projected area can be obtained by using paper with grids, or by cutting out a tracing of particle and weighing. By determining the area per unit weight of the paper, the weight of a tracing may be converted into an area measurement. The popularity of this laborious manual mode of dimensional measurement has declined significantly with the introduction of image analyzers. When a video camera is attached to a microscope, the image obtained on a high-resolution monitor may be digitized and analyzed using a computer (Fig. 1). Information on the breadth, length, perimeter, and area of particles can be determined very rapidly. The degree of accuracy of such measurements depends on the clarity of image available and the separation of particles from one another.

There are a large number of transformation models that can be used to analyze the image dimensional parameters in the determination of particle shape. Some methods require additional information on particle surface area, volume, or thickness to give better estimates of shape, but for most purposes, a simple approach is often preferred. The common treatment of data—namely, breadth, length, perimeter, and area—to reflect the particle shape [1,2] is given as follows:

$$\text{Aspect or elongation ratio} = \frac{\text{length}}{\text{breadth}} \quad (1)$$

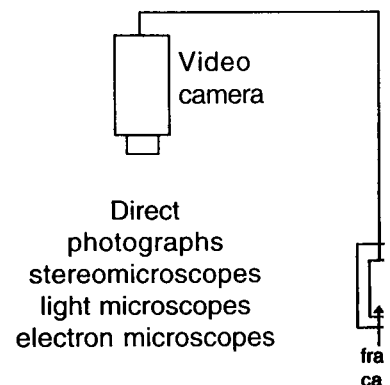


Fig. 1 Image analysis system.

$$\text{Bulkiness factor} = \frac{\text{length}}{(\text{length})^2}$$

$$\text{Form factor} = \frac{4\pi(\text{area})}{(\text{perimeter})^2}$$

The elongation ratio is very useful for shape to an elongated form. The measure of sphericity, and a measure of bulkiness factor gives an indication of the particles give rise to low

For many users of image analysis models is usually available on many users is not the mathematical rather, the selection of an appropriate Fourier shape analysis and fractal allow further treatment of image or more measurement techniques also been used for particle shape analysis systems include Data Translation, Mahwah, New Jersey, and SynGene

## B. Particle Size

There is much literature on the distribution. With the abundance of methods, a less-experienced operator

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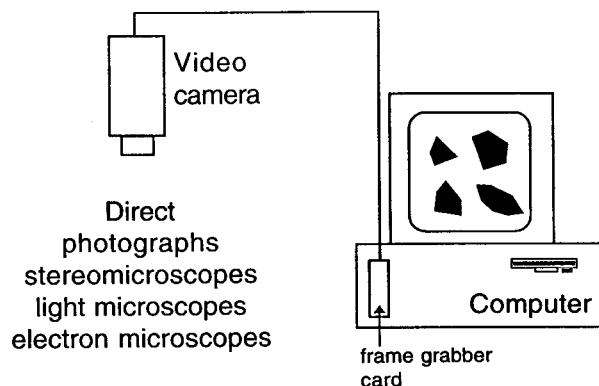


Fig. 1 Image analysis system.

$$\text{Bulkiness factor} = \frac{\text{area}}{(\text{length} + \text{breadth})} \quad (2)$$

$$\text{Form factor} = \frac{4\pi(\text{area})}{(\text{perimeter})^2} \quad (3)$$

The elongation ratio is very useful for assessing deviation from a spherical shape to an elongated form. The form factor, on the other hand, gives a measure of sphericity, and a perfect sphere has a form factor value of unity. The bulkiness factor gives an indication of solidity, and large indentations on the particles give rise to low values [3].

For many users of image analyzers, a wider array of mathematical models is usually available on the software. The problem that confronts many users is not the mathematical treatment of image analysis data, but rather, the selection of an appropriate transformation model. Procedures for Fourier shape analysis and fractal measurement [4–7] are also available to allow further treatment of image analysis data. Indirect methods using two or more measurement techniques, such as sedimentation and sieving have also been used for particle shape determination [8]. Vendors for image analysis systems include Data Translations, Marlboro, Massachusetts; Edax, Mahwah, New Jersey, and Synoptics, Cambridge, United Kingdom.

## B. Particle Size

There is much literature on the measurement of particle size and size distribution. With the abundance of information on particle sizing and sizing methods, a less-experienced operator can find it daunting to decide which

method is the best. After completion of a measurement, the task of data interpretation and validation of the accuracy and reliability of measurements can be difficult. Often, standards are used for comparison, and the information obtained from these standards is used for calibration of the size-measuring system. Standards used are very often ideal particles, with a high degree of sphericity and a narrow size distribution. The real samples for size analysis are often not spherical and can have a considerably wide size distribution. Therefore, it is important to consider all results with some suspicion and in a comparative perspective, which depends on the standard calibrator used and the method of measurement. Proper and stringent development of the method for size measurement should be carried out to ensure reliability, reproducibility, and sensitivity of the measurement method.

The present discussion on the particle-sizing methods does not attempt to establish yet another theory and practice guide on particle sizing, but to review the popular methods of particle sizing, their problems and their usefulness in providing information valuable to a formulator. Little attempt will be made to explain the theories of various sizing methods, for they are dealt with in many other comprehensive publications on this subject [8–10].

### 1. *Microscopy*

Microscopy is a very old technique capable of sizing fine powders accurately. Nowadays, it is considered to be an unpopular method to use mainly because of the tedium in measurement and the availability of more sophisticated and easy-to-use particle sizers. Nevertheless, microscopy still presents as the most direct method of particle size analysis. However, as a particle sizer, a minimum of at least 625 particles must be measured for computation of reasonable size statistics [11]. In a particle-sizing laboratory, the value of the microscope usually is not as a primary equipment for particle sizing, but rather, for the preliminary examination of the size distribution of a powder sample before the use of a less direct particle size analyzer. The estimation of particle size characteristics obtainable from the microscope would certainly provide a rough guide for the setting of an automated particle sizer to the correct sizing range, or for checking if the size analysis data obtained is within an expected range.

Unlike other particle sizers, the microscope gives the operator a clear visual outline of each individual particle being measured. In addition, the material may be presented in its normal form, dry, or in a liquid medium. Particles that are aggregated can be identified and will not be measured as a single entity. Problems associated with microscopic sizing lie not only in the tedious nature of the technique, but also in the slide sample preparation, optical resolution, and operator bias.

Sample preparation for microscopic sizing is a critical step. The distribution of particles on the slide must be uniform. The material is to be made as a suspension in a liquid medium. The particles through dissolution or dispersion before transferring onto a slide. The presentation of the area of slide must be in a systematic and orderly manner. The operator must know the size of the sample. There is an intrinsic problem when presented always find the same size. This involves measuring a particle from a two-dimensional. Thus, flakes or disc-shaped particles the dimension(s) to measure need a grid or graticule be used. An area graticule is used for area determination. Orientation of particles on powders onto adhesive before viewing. The slide which is then sectioned for viewing. This is an already tedious technique even with the use of a microscope.

Clarity is always a problem in microscopy. The limit of light microscope optics, the resolution, may also play a part. There is a tendency to fringe effects around particles. Microscopic imaging techniques can improve viewing. In some cases, the use of dyes can enhance contrast and background.

An operator with good technique can obtain results with minimal systematic error. The accuracy of microscopic determination is a tendency for operators to pay attention to the results are less likely to miss them. No operator is perfect they also pose problems by being too small appearing as clumps. However, the influence of the smaller influence.

Automation of the microscopic sizing technique [12] and progress in the use of finally, computer image digitization. This discussion on particle shape has been a long time. Information for particle size and shape is a key factor of data for deriving shape factors. Microscopy is scanning electron microscopy. Directly from the video image of particles. Sizing systems may also be used.

of a measurement, the task of data accuracy and reliability of measurements used for comparison, and the information used for calibration of the size-very often ideal particles, with a high distribution. The real samples for size have a considerably wide size distribution. Consider all results with some suspicion, which depends on the standard measurement. Proper and stringent measurement should be carried out to sensitivity of the measurement

Particle-sizing methods does not attempt to give a guide on particle sizing, but to identify their problems and their use to a formulator. Little attempt will be made in sizing methods, for they are dealt with in other publications on this subject [8-10].

Microscopy of sizing fine powders is an unpopular method to use mainly because of the availability of more sophisticated methods. Nevertheless, microscopy still provides a means for particle size analysis. However, as a minimum, 25 particles must be measured for statistical significance [11]. In a particle-sizing laboratory, microscopy is a primary equipment for particle size determination of the size distribution of a sample. It is a direct particle size analyzer. The results are obtainable from the microscope. For the setting of an automated particle size analyzer for checking if the size analysis is acceptable.

Microscopy gives the operator a clear view of the particles being measured. In addition, the particles can be in solid form, dry, or in a liquid medium. Particles that are agglomerated and will not be measured as individual particles in microscopic sizing lie not only in the sample but also in the slide sample preparation,

Sample preparation for microscopy must ensure a representative distribution of particles on the slide to be used for sizing. When powder material is to be made as a suspension, there should be no loss of smaller particles through dissolution nor loss of large particles by sedimentation before transferring onto a slide. It is best to wet a sample on the slide itself. Presentation of the area of slide specimen for sizing must be carried out in a systematic and orderly manner by moving the slide to view different areas of the sample. There is an intrinsic orientation problem because particles when presented always find their most stable orientation. Microscopy involves measuring a particle from only the top view and measurement is two-dimensional. Thus, flakes or discoids will tend to be oversized. Decision on the dimension(s) to measure needs to be made should a linear eyepiece graticule be used. An area graticule may also be employed for projected area determination. Orientation problems may be overcome by dispersing powders onto adhesive before viewing or setting particles in plastic or wax, which is then sectioned for viewing. These techniques will definitely make an already tedious technique even more so.

Clarity is always a problem as sizes of particles approach the lower limit of light microscope optics, which is about 1  $\mu\text{m}$ . The quality of lenses may also play a part. There is often a tendency to oversize slightly owing to fringe effects around particles. Various microscope accessories and lighting techniques can improve viewed image resolution to varying extents. In some cases, the use of dyes can help improve the contrast between particle and background.

An operator with good technique is necessary to obtain reliable results with minimal systematic errors. Operator technique can influence accuracy of microscopic determination of particle size. There is a natural tendency for operators to pay greater attention to large particles as they are less likely to miss them. Not only do small particles tend to be missed, they also pose problems by being hidden by the larger particles or appearing as clumps. However, in volumetric terms, small particles have a smaller influence.

Automation of the microscopic technique began with an image-shearing technique [12] and progressed to image projection and measurement and, finally, computer image digitization and image analysis [13]. The preceding discussion on particle shape has covered the use of image analysis. Information for particle size and size distribution is easily obtained from the set of data for deriving shape factor of the particles. An extension of light microscopy is scanning electron microscopy. Measurements may be made directly from the video image or by photomicrographs. Attached image analysis systems may also be used for sizing.



## 2. Sedimentation

Sedimentation techniques for particle sizing and classification have been in use a long time. In recent years, however, the success of light-scattering particle sizers has effectively eroded away the market for sedimentation-based particle sizers. The sedimentation technique for sizing is based on the settling of particles under gravity described by Stokes' law. For a particle of diameter  $d$  and density  $\rho_1$ , under the force of gravity  $g$  in a fluid of viscosity  $\eta$ , and density  $\rho_2$ , at its terminal velocity  $v$ , the accelerating force caused by gravity is balanced by the viscous drag and

$$v = \frac{d^2 g (\rho_1 - \rho_2)}{18\eta} \quad (4)$$

The Andreasen pipette, introduced in the 1920s, is perhaps the most popular manual apparatus for sampling from a sedimenting suspension. Determination of the change in density of the sampled particle suspension with time enables the calculation of size distribution of the particles. As Stokes' law applies only to spherical particles, the nonspherical particles give a mean diameter referred to as Stokes' equivalent diameter. The size range measurable by this method is from 2 to 60  $\mu\text{m}$  [8]. The upper limit depends on the viscosity of liquid used, and the lower limit is due to the failure of very small particles to settle as these particles are kept suspended by Brownian motion.

An improvement of the Andreasen pipette method is to use a pan attached to a sensitive balance that records the changes in weight of the pan as increasing amount of suspending particles settles on it. Later, sedimentation techniques using light extinction by changes in turbidity of the suspension and x-ray analysis were introduced for more sensitive and rapid measurements.

The introduction of centrifugal sedimentation makes the technique capable of determining the distribution of particles smaller than 5  $\mu\text{m}$ . The lower limit depends on the centrifugal velocity. The time of analysis is reduced drastically; and multiple samples in cells can be analyzed simultaneously.

## 3. Sieving

Sieving is probably the oldest method of sizing, used initially for particle classification, rather than size analysis. The introduction of high-quality standardized woven-wire sieves in a square-root-of 2 progression, starting from 75  $\mu\text{m}$ , has helped establish sieving as a widely used particle-sizing method, especially for the larger particles. Conceptually, particle sizing by sieving is

easily understood as the difference in weight-based size fractions, giving

The process of sieving involves arranging the sieves from the largest aperture to the smallest. The sieves with a lid and receiver are arranged in a stack that may gyrate, oscillate, or vibrate. The shakers are vibrators. It is important to complete the sieving. This is common for a further change in the weight of the material. The additional sieving time is given. The amount that the amount present after weighed.

In size analysis using sieves, the size of a given sieve is not an absolute. It is permitted to pass through. The size of the particle and following the maximum tolerance. (1976), particles from 55 to 95  $\mu\text{m}$ —aperture sized sieve. Particles with a lower cross-sectional area. A particle, will pass through an aperture. A sectional profile. Woven sieves are made of much higher precision. Sieves can be made using etching methods. Electroformed micromesh sieve. Drilled or punched circular holes. Sizing larger particles, generally.

Size analysis by sieving is a common method. Problems with dust pollution. It needs to be considered. In addition, Apertures may be blanked by powders, aggregation of powders, charges, can give inaccurate results. It is also unreliable data. It is also itself does not bring about size.

Because sieving fine powders is difficult due to the cohesive nature of such powders, sieving by suspending the powder in a liquid is more efficient. However, the procedure involves the additional drying of the size fractions. It starts with the finest mesh to the coarsest mesh, followed by classifying the powder into the mesh.

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easily understood as the different meshes classify the particles to different weight-based size fractions, giving rise to the frequency distribution.

The process of sieving involves a nest of sieves, usually five to eight, arranged from the largest aperture to the finest followed by a receiving pan. The sieves with a lid and receiving pan are then placed on a sieve shaker that may gyrate, oscillate, or vibrate the sieves. The most commonly used shakers are vibrators. It is important to determine the time required for completion of sieving. This is commonly taken as the time at which there is no further change in the weight of material retained on each sieve after additional sieving time is given. The load for sieve analysis should be sufficient that the amount present after sieving on each mesh can be accurately weighed.

In size analysis using sieves, it must be borne in mind that the aperture size of a given sieve is not an absolute cutoff value for the size of particles permitted to pass through. The permitted aperture tolerance is much wider and following the maximum tolerance allowed by the British Standard 410 (1976), particles from 55 to 95  $\mu\text{m}$  may go through or be arrested by a 75- $\mu\text{m}$ -aperture sized sieve. Particles tend to pass through based on their narrower cross-sectional area. An elongated particle, such as a rod-shaped particle, will pass through an aperture just larger than its minimum cross-sectional profile. Woven sieves can be made down to about 30  $\mu\text{m}$ . Finer sieves of much higher precision from 100  $\mu\text{m}$  down to a few microns can be made using etching methods, and these sieves are often referred to as electroformed micromesh sieves. Sieves with bases that have accurately drilled or punched circular holes, instead of woven mesh, are available for sizing larger particles, generally about 500  $\mu\text{m}$  and larger.

Size analysis by sieving is a relatively slow process, and there may be problems with dust pollution. For many drugs, the safety of the operator needs to be considered. In addition, wire mesh stretches with repeated use. Apertures may be blanked by improper or inadequate washing. For fine powders, aggregation of powders, caused by cohesive or electrostatic charges, can give inaccurate results. Inadequate sieving time will also produce unreliable data. It is also important to ensure that the sieving process itself does not bring about size reduction.

Because sieving fine powder in a dry state may be a problem owing to the cohesive nature of such powder and long sieving time required, wet sieving by suspending the powder in a suitable liquid can improve sieving efficiency. However, the procedure becomes more tedious. It now requires the additional drying of the sized fractions. It is recommended that sieving starts with the finest mesh to remove the fines with a volume of liquid, followed by classifying the powder retained with the largest to the smallest mesh.

Air-jet sieving is a much more popular method for sizing fine powders smaller than 75  $\mu\text{m}$  than wet sieving. It involves the use of a vacuum pump to remove air from the underside of a sieve. Air current is also supplied from the underside of the sieve through a rotating arm of jets, which helps unclog the mesh. A collecting cyclone may be attached in the vacuum line to collect the fines; in-line filters also may be used to collect the fines. Air-jet sieving is usually used as a one-mesh sieving. For information of size distribution, composite size distribution may be obtained from separate air-jet sieving operations using different meshes for samples of the same powder.

A common point of discontent with size analysis using sieves is that the process requires quite a bit of preparatory work, weighing, and subsequent washing. Yet, a typical analysis would yield only 7 to 8 points on the size distribution and this may not be sufficiently discriminating. Nevertheless, sieving is a straightforward and robust technique suitable for a wide variety of fine to very coarse powders. Material properties, such as density, optical property, water-solubility, or conductivity, are not required for computation of the particle size.

#### 4. Electrical Sensing

The electrical-sensing zone principle, which is more commonly known as the Coulter principle, is based on a simple electrical property; namely, that the electrical resistance between two compartments containing an electrolyte and connected by an aperture is proportional to the electrical-conducting area of the aperture. Figure 2 illustrates the basic Coulter principle. By drawing electrolyte from one compartment to the other, particles streaming

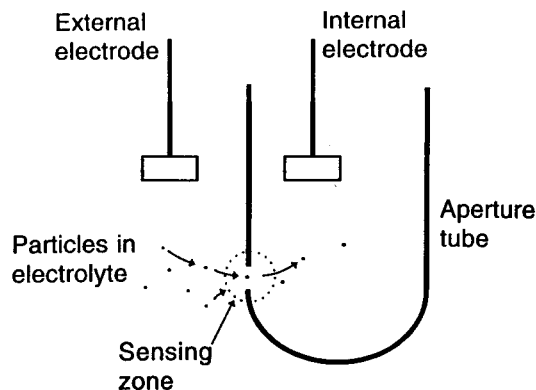


Fig. 2 The Coulter principle.

through will decrease the conductance. Based on the resistance, the number of particles through the aperture is proportional to the volume of the sample. A counter can analyze a large number of particles.

The detectable particle size range is determined by the aperture diameter. Each aperture tube is effective for a specific nominal diameter. Apertures are available in a range of diameters. Before use, it is necessary to calibrate the counter with a sample containing monosize spherical particles of known aperture diameter.

When working with small particles, the aperture diameter is a limiting factor. With large apertures for coarse particles, the resistance may give rise to sizing errors. Sizing is nonconductive and nondestructive. The results obtained may be much smaller than the actual size. In addition, the powder for sizing must be properly dispersed in the electrolyte. The particles must not agglomerate nor dissolve in the electrolyte. The proper dispersion of powder is a critical factor in the range acceptable. A high concentration of powder, owing to coincidence, where two or more particles are counted as one, will increase the counting time.

#### 5. Light Scattering

There has been a tremendous increase in the use of light scattering techniques for particle sizing. In the past few years, light scattering has taken a lion share of the number of manufacturers of instruments. It is also a hand in convincing manufacturers. However, it is unfair to ascribe the success to just its marketing. Light scattering is a simple technique. Samples are indeed much easier to handle. Measurement time is short, and the results are reproducible particle size information.

Without dwelling on the details, the principle of using this principle can be reduced to three basic terms: determining particle size down to a certain limit, diffraction, and the third, for scattering. A schematic diagram of light scattering is shown in Fig. 3.

lar method for sizing fine powders involves the use of a vacuum pump sieve. Air current is also supplied by a rotating arm of jets, which helps to break up agglomerates. The sieve may be attached in the vacuum line and used to collect the fines. Air-jet sieving. For information of size distribution may be obtained from separate air-jet sieves for samples of the same pow-

size analysis using sieves is that laboratory work, weighing, and subsampling would yield only 7 to 8 points on the size distribution. Nevertheless, this technique is suitable for a wide range of material properties, such as density, particle shape, and activity, are not required for com-

ch is more commonly known as the electrical property; namely, that particles containing an electrolyte solution are conductive to the electrical-conducting principle of the basic Coulter principle. By contrast to the other, particles streaming

through will decrease the conducting area of the aperture. By fast, time-based tracing of the resistance, resistance pulses coinciding with the passage of particles through the aperture will be obtained. The amplitude of the pulse is proportional to the volume of particle. With a pulse analyzer, the Coulter counter can analyze a large number of particles within a short time.

The detectable particle size range depends on the aperture tube used. Each aperture tube is effective over a size range of about 2–40% of its nominal diameter. Apertures of sizes from 15 to 4000  $\mu\text{m}$  are available. Before use, it is necessary to calibrate the equipment with a standard latex, containing monosize spherical particles of mean size within 5–20% of the aperture diameter.

When working with small apertures, aperture blockage may be a problem. With large apertures for sizing large particles, settling of the large particles may give rise to sizing errors. It is important that the material for sizing is nonconductive and nonporous. For porous particles, sizing values obtained may be much smaller than that derived by visual inspection. Before addition of the powder for sizing, it is necessary to ensure a low background count. When dispersed in the electrolyte, the powder particles must not flocculate nor dissolve in the electrolyte solution. Care must be taken to ensure proper dispersion of powder. The concentration of particles must be within the range acceptable. A higher concentration will result in higher errors owing to coincidence, whereas low concentration will necessitate a longer-counting time.

## 5. Light Scattering

There has been a tremendous growth in the application of light-scattering techniques for particle sizing in recent years, and light-scattering particle sizers have taken a lion share of the market for particle sizers. The large number of manufacturers of instruments using light-scattering techniques has also a hand in convincing many laboratories of their need for such a sizer. However, it is unfair to ascribe the recent popularity of light-scattering sizing to just its marketing. Light-scattering particle sizers for both wet and dry samples are indeed much easier to use and are highly efficient. The measurement time is short, and the method is able to produce detailed and reproducible particle size information.

Without dwelling on the theories of light scattering, particle sizers using this principle can be roughly divided into three groups: two for determining particle size down to about 1  $\mu\text{m}$  using light obscuration and laser diffraction, and the third, for submicron particle size using photon correlation spectroscopy. A schematic diagram of the various techniques of light scattering is shown in Fig. 3.

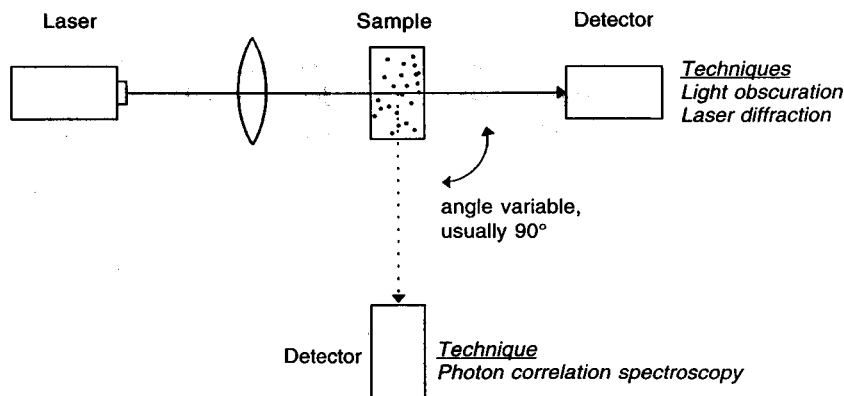


Fig. 3 Schematic diagram for light-scattering particle sizing.

Light obscuration or blockage technique involves measuring particles singly. The passage of a particle across the light beam produces a reduction in the amount of transmitted light, which is detected by a sensor directly opposite the incident light. The pulses are then classified giving the frequency distribution. The degree of light diffraction, opacity, and orientation of the particle as it passes the light beam can affect the extent of light blockage and may affect measurement accuracy.

As a small particle passes through a beam of light in a laser diffraction sizer, it will scatter light, which will be directed onto a diode array detector directly opposite the incident light. The detector has a series of photodiodes arranged outward from a central photodiode detector. Because the intensity of the light scattered decreases as the scatter angle increases, photodiode elements are generally larger as they progress further from the center. Calculations for particle size and size distribution involve rather complex mathematics. Simply put, sizing of a particle is based on the angle of diffracted light, with small particles diffracting at wider angles than larger particles. Thus, from the light-scattering pattern, information on the size distribution of the particles can be obtained through a series of complex calculations.

Sample presentation for light obscuration sizer involves the dispersion of the particles in a liquid medium, as used in the electrical-sensing sizer. The main difference is that light obscuration sizer may operate in the absence of an electrolyte. For laser diffraction, sizing may be carried out both on particles dispersed in fluid as well as on dry powders using dry powder

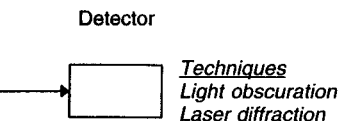
feeders. Laser diffraction is also used for aerosol sprays.

The possibility of measuring the size of powders in their dry state, with a very short timespan, has attracted attention. Laser diffraction sizer is an effective method for accurate size distribution information. Sizing of some powders using laser diffraction sizer can be fraught with problems. Results are the poor control of angle of diffraction, powder particles that fragment, variable rate of introduction of particles, possible segregation of powder particles depositing on the lens. The sizer and very small particles can be problematic. Particles will adhere onto their surfaces. The size of the smaller particles can be affected. The feed rate of particles for sizing is critical. The humidity of the atmosphere

## 6. Photon Correlation Spectroscopy

The measurement of submicron particles using photon correlation spectroscopy enables particles from a few nanometers to several micrometers to be measured. The measurement principle is based on the scattered light intensity fluctuations, which are the result of Brownian motion. Large particles will diffuse more slowly, resulting in a slower rate of decay in the intensity fluctuations. The time point will depend on the size of the particles. The size is computed using complex calculations of the scattered light (not the intensity) and rates of decay. Multiple angles of measurement improve the quality of the size distribution.

Although the photon correlation spectroscopy is a new instrument for the sizing technology, it is still generally fall into the submicron range. The main problem is in the evaluation of polymer particles. Suppliers for both laser diffraction and photon correlation spectroscopy are Coulter Electronics, Miami, FL and Malvern Instruments, Worcester, MA.



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feeders. Laser diffraction is also very useful for sizing aerosol particles and sprays.

The possibility of measuring the particle size and size distribution of powders in their dry state, with an acceptable level of accuracy and in a very short timespan, has attracted many laboratories. For many users, the laser diffraction sizer is an efficient equipment for producing detailed and accurate size distribution information of the powder particles. However, the sizing of some powders using a dry powder feeder with the laser diffraction sizer can be fraught with problems. Possible causes of nonreproducible results are the poor control of ambient humidity, cohesive nature of the powder, powder particles that fragment easily, large-size span of the particles, variable rate of introduction of particles during the measurement period, possible segregation of powders during introduction, and stray powder particles depositing on the lens. The sizing of a powder composed of very large and very small particles can be problematic because a portion of the small particles will adhere onto their larger counterparts. The complete dislodging of the smaller particles can be an extremely difficult task and, with different feed rate of particles for sizing, different results may be obtained. In addition, the humidity of the atomizing air can also affect sizing results.

## 6. Photon Correlation Spectroscopy

The measurement of submicron particles had been difficult until the introduction of photon correlation spectroscopy for particle sizing. This technique enables particles from a few nanometers to a few micrometers to be measured. The measurement principle involves the determination of fluctuations in the scattered light intensity at an angle (see Fig. 3). These fluctuations are the result of Brownian motion of the suspended particles in the liquid. Large particles will diffuse more slowly than smaller ones; therefore, the rate of decay in the intensity of scattered light at a particular measuring point will depend on the size of the particle. The particle size distribution is computed using complex calculations and approximations from the intensities of the scattered light (normally at 90° to the incident beam) and their rates of decay. Multiple angle measurements are sometimes applied to improve the quality of the size parameters obtainable.

Although the photon correlation sizer represents a very interesting instrument for the sizing technologist, powders for granulation do not generally fall into the submicron range. The few possible uses of this instrument is in the evaluation of polymeric materials employed for binding and coating. Suppliers for both laser diffraction and scattering particle sizers include Coulter Electronics, Miami, Florida; Hiac/Royco, Silver Spring, Maryland; and Malvern Instruments, Worcs, United Kingdom.

### C. Particle Surface Area

Surface area measurement is usually carried out by either gas permeability or adsorption. The technique of gas permeability depends on measuring the resistance to gas flow through a packed bed of particles. It is important that packing of the bed is uniform, and from the volumetric flow rate of the gas through and pressure drop across the bed, the specific surface area of the powder can be calculated. The measurement of specific surface area by gas permeability does not take into account the very small pores or fissures, because the flow of gas is not hindered as it passes over them. More accurate measurements can be made by measuring gas flow under reduced pressure, but still, the accuracy cannot match that obtainable by gas adsorption if the total area to be determined includes those of the fine pores. Although gas permeability gives a lower specific area for a powder, compared with gas adsorption, the value obtained is sometimes more useful in explaining factors such as lubricity and flow that would not involve the micropores present in the particles.

Gas adsorption is carried out by placing a powder sample in a chamber and evacuating the air within. The latter process is commonly referred to as degasing. After achieving a very high vacuum, known volumes of an adsorbing gas are introduced. From the knowledge of pressures and temperatures before and after introduction of the adsorbing gas, usually nitrogen, calculations of total sample surface area can be made. The surface area determination by gas adsorption is based on a simple principle. From Avogadro's number, a known volume of air at a certain temperature and pressure contains a determinable number of molecules. When varying volumes of gas are introduced to a degased sample, the small pressure changes in the chamber are recorded, and by using a calculation technique, known as the BET method, the initial numbers of gas molecules that are adsorbed onto the surface, forming a monolayer, can be calculated. Thus, the surface area covered by the gas molecules can be determined by multiplying the number of molecules needed by the surface area occupied per molecule. Samples are usually cooled to a low temperature using liquid nitrogen. There are variations in the technique for gas adsorption by different instrument manufacturers [14].

In addition to determining the specific surface area, pores smaller than 50 nm may also be characterized by gas adsorption. Distribution of larger pores, 0.003–400  $\mu\text{m}$ , can be determined by mercury intrusion porosimetry technique, in which the volume of mercury intruded under pressure represents the volume of pores, the entrant diameter of which can be calculated from the applied pressure [15]. Main suppliers of equipment for surface and porosimetry include Quantachrome, Syosset, New York, and Micromeritics, Norcross, Georgia.

### III. SOLUBILITY

The solubilities of drugs and excipients are important properties because they affect the rate of release into the dissolution medium. The solubility of the pharmaceutical product must first be in solution to be absorbed. If the solubility of the drug is less than desirable, it may be necessary to use another more soluble formulation or to use another more soluble medium. Hence, the determination of solubility is an important aspect of a formulation.

The solubility of a material can be determined by a number of methods. The most common solubility method, which employs a saturated solution, is obtained by adding a known amount of solvent for a prolonged period, until equilibrium is attained. As a guide, stirring the solution for 24 hours, achieving equilibrium. The saturated solution is then cooled to the required temperature. The saturated solution for some materials may be unstable, and caution should be taken. A portion of the saturated solution is then removed with the aid of a syringe and analyzed at time intervals. The determination of solubility for different samples have the same results, and the final value thus obtained is the same. The determination of solubility by other methods, such as UV spectrophotometry, gravimetric or volumetric methods, is also possible.

The following precautions should be taken to obtain reproducible solubility values:

- The material and solvent should be of high purity.
- The temperature must be controlled.
- It is essential that the solution be stirred continuously to ensure that the solution is saturated.
- The saturated solution should be analyzed immediately after preparation.
- The method of assay should be standardized.

A sound understanding of the solubility of drugs and excipients is pertinent in explaining the characteristics of a formulation.

### III. SOLUBILITY

The solubilities of drugs and excipients are an important physicochemical property because they affect the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product. It must be remembered that a drug must first be in solution to be absorbed into the blood circulation. If the solubility of the drug is less than desirable, steps must be taken to improve its solubility or to use another more soluble drug form. Those excipients that are poorly soluble in water might retard the release of drug into the dissolution medium. Hence, the determination of drug and excipient solubilities constitutes an important aspect of a formulation study.

The solubility of a material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material. The saturated solution is obtained by stirring an excess of the material in the solvent for a prolonged period, at a constant temperature, until equilibrium is attained. As a guide, stirring the mixture overnight is usually adequate for achieving equilibrium. The saturated solution can also be obtained by warming the solvent with an excess of the material and allowing the mixture to cool to the required temperature. This, however, may produce a supersaturated solution for some materials; therefore, heating should be applied with caution. A portion of the saturated solution obtained by either method is then removed with the aid of a syringe through a membrane filter at different time intervals. The determination is completed only if at least two successive samples have the same results, indicating that equilibrium is attained. The final value thus obtained is the solubility of the material. The material present in the sample of saturated solution may be assayed by a variety of methods, such as UV spectrophotometry, electrical conductivity measurement, gravimetric or volumetric analysis, and chromatographic methods.

The following precautions should be observed to obtain accurate and reproducible solubility values:

- The material and solvent must be pure.
- The temperature must be properly controlled.
- It is essential that some undissolved material is present in the solution to ensure that the solution obtained is saturated.
- The saturated solution used for assay must be free from undissolved material.
- The method of assay must be reliable.

A sound understanding of the factors affecting solubilities of materials is pertinent in explaining the changes in solubility under different conditions.



These factors, therefore, can be employed to improve the solubility and bioavailability of various drugs.

### A. Nature of Solvent

Some materials dissolve very readily in a solvent, whereas others dissolve sparingly. The solubility of the material in a given solvent depends on the ability of the solvent to overcome the forces that bind the atoms or molecules of the material. Studies have shown a definite correlation between the solubility and the molecular structures of the material and solvent. The greater the similarity in molecular structure, the higher would be the solubility of the material in the solvent. As a rule, polar materials dissolve readily in polar solvents, whereas nonpolar materials dissolve in nonpolar solvents. Materials with both polar and nonpolar groups in their molecules may dissolve in polar solvents, but their solubilities tend to decrease as the proportion of nonpolar groups in the molecule increases.

Many materials have poor solubilities in water and often pose a problem in the formulation of pharmaceutical products. Addition of another solvent, in which these materials are more readily soluble, will increase the concentration of the materials in the solution. This additional solvent is known as a cosolvent; common examples include glycerin, sorbitol, propylene glycol, and polyethylene glycols. The proportion of cosolvent required varies from system to system.

### B. Temperature

The solubilities of most materials increase with rising temperature owing to their endothermic dissolution process. Similarly, the solubilities of materials that exhibit exothermic dissolution decrease with rising temperature. The relation between solubility and temperature is expressed by solubility curves. Three typical solubility curves are shown in Fig. 4.

A material for which solubility increases with rising temperature exhibits a continuous curve with a positive slope (see curve A), whereas that for which solubility decreases with rising temperature exhibits a negative slope (see curve B). Some solubility curves show an abrupt change in slope at certain temperatures (see curve C). This phenomenon is attributed to the change in nature of the material at the temperature at which the slope changes direction. For example, the solubility curve C is derived from a material that can exist in two forms. The curve shows that form I is converted to form II at temperature  $t$ . The dissolution of form I in water is endothermic, which explains the increasing solubility of the material with rising temperature until  $t$ . Above this temperature, form I is converted to

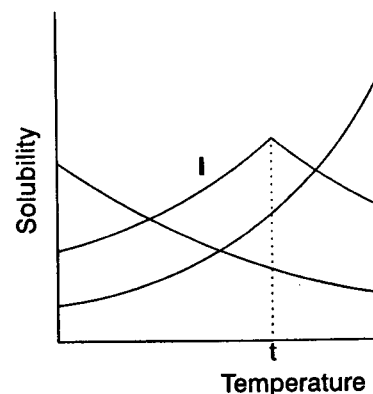


Fig. 4 Typical solubility curves.

form II, which exhibits exothermic dissolution. The solubility curve, therefore, changes from increasing to decreasing at temperature  $t$ .

### C. Crystal Characteristics

Materials may exist as amorphous or crystalline forms. Some materials, such as cortisone, tetracycline, and many others, can exist in more than one crystalline form, a phenomenon known as *polymorphism*. The different crystalline forms, or *polymorphs*, exhibit different degrees of solubility. Crystalline substances may be converted to the solvent from which crystalline forms are called *solvates*. If the solvates are not *hydrated*.

The different forms of a material may have different solubilities. In general, the amorphous substance is more soluble than the crystalline forms, the metastable form is more soluble than the stable polymorphs. Hydrates are more soluble in water than their anhydrous forms. The solubility of the nonaqueous solvates also varies with the nature of the forms.

### D. Particle Size

It is important to distinguish between the solubility of a material. Unlike intrinsic solubility, the solubility of a material is a function of particle size.

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a solvent, whereas others dissolve in a given solvent depends on the es that bind the atoms or molecules finite correlation between the sol- e material and solvent. The greater higher would be the solubility of olar materials dissolve readily in als dissolve in nonpolar solvents. groups in their molecules may dis- ies tend to decrease as the propor- ncreases.

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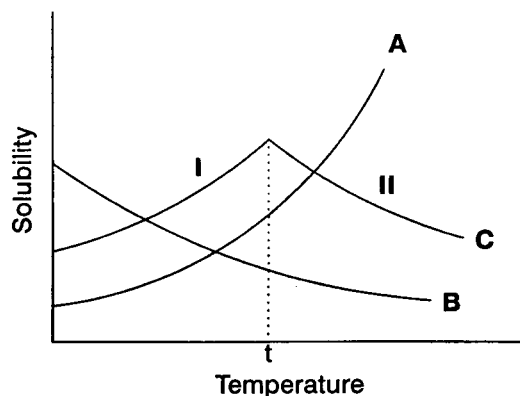


Fig. 4 Typical solubility curves.

form II, which exhibits exothermic dissolution. The slope of the solubility curve, therefore, changes from positive to negative as the temperature exceeds  $t$ .

### C. Crystal Characteristics

Materials may exist as amorphous or crystalline substances. Some materials, such as cortisone, tetracycline, sulfathiazole, and chloramphenicol palmitate, can exist in more than one crystalline form, and this property is described as *polymorphism*. The different crystalline forms, which are known as *polymorphs*, exhibit different degrees of stability. The lattice structure of the crystalline substances may be altered by the incorporation of molecules of the solvent from which crystallization occurs. The resultant crystals obtained are called *solvates*. If the solvent is water, the crystals are said to be *hydrated*.

The different forms of a material have varying solubilities. The amorphous substance is more soluble than the crystalline counterpart. Among the crystalline forms, the metastable polymorphs are generally more soluble than the stable polymorphs. Hydrated crystals tend to exhibit a lower solubility in water than their anhydrous form. On the contrary, the aqueous solubilities of the nonaqueous solvates are often higher than those of the unsolvated forms.

### D. Particle Size

It is important to distinguish equilibrium solubility from intrinsic solubility of a material. Unlike intrinsic solubility, equilibrium solubility is not affected

by the particle size of the material. The solubilities of materials reported in the literature generally refer to the equilibrium solubilities. The method of determining equilibrium solubility is given in an earlier section.

The intrinsic solubility of a material is dependent on the particle size of the material. Smaller particles have higher intrinsic solubilities, compared with their larger counterparts. This is aptly explained by the existence of a higher interfacial free energy on smaller particles, resulting in a thermodynamically unstable system that is corrected by greater dissolution of the particles and production of a supersaturated solution. The increase in intrinsic solubility with decrease in particle size, however, ceases when the particles have a very small radius, and any further decrease in particle size causes a decrease in intrinsic solubility.

### E. pH

The solubility of a material will be affected by the pH of the liquid medium if the material is acidic or basic. For example, a weakly acidic drug is more soluble in an alkaline solution, whereas a weakly basic drug is more soluble in an acidic solution. This phenomenon is due to the formation of more soluble salts as a result of acid-base reaction. Conversely, the weakly acidic drug will precipitate from the solution if the pH is lowered by the addition of an acid, whereas the weakly basic drug will precipitate from the solution if the pH is raised by the addition of an alkali. The precipitation is a result of the conversion of the drug in solution to the less soluble nonionized form.

The relation between pH and solubility of material is given by Eqs. (5) and (6). These equations, which are modified from the Henderson-Hasselbalch equation are useful in the estimation of the solubility of materials under different pH conditions.

$$\text{For acidic materials, } \text{pH} = \text{p}K_a + \log \frac{S - S_0}{S_0} \quad (5)$$

$$\text{For basic materials, } \text{pH} = \text{p}K_a + \log \frac{S_0}{S - S_0} \quad (6)$$

where  $S$  is the overall solubility of the drug and  $S_0$  is the solubility of its nonionized form.

### F. Additives

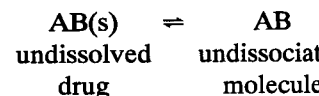
Additives refer to other substances incorporated into the solvent in which the drug is dissolved. The drug in the solution may exist as ionized or nonionized forms. Drugs that dissociate in the solvent to form ions are de-

scribed as ionizable, whereas the others do not. Among the additives to the drug. The effects of additives on the nature of the drug as well as the additives will be classified as nonelectrolytes.

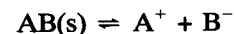
#### 1. Effect of Common Ions on Ionizable Drugs

The solubility of a sparingly soluble drug possesses an ion similar to the drug, the common ion effect, can be explained.

The equilibrium of a saturated drug is represented as follows:



If the material is sparingly soluble and the particle size is sufficiently small to assume equilibrium, therefore, may be expressed as



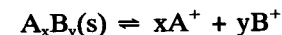
From the law of mass action, the equilibrium reaction is given by the following

$$K = \frac{[\text{A}^+][\text{B}^-]}{[\text{AB(s)}]}$$

where the square brackets indicate the concentrations of the components. Because the concentration of the solid is constant, Eq. (9) can be rewritten as

$$K'_s = [\text{A}^+][\text{B}^-]$$

where  $K'_s$  is a constant known as the solubility product. Some drugs have molecules that dissociate into ions. The equilibrium and solubility product can be expressed as



$$K'_s = [\text{A}^+]^x [\text{B}^-]^y$$

solubilities of materials reported in equilibrium solubilities. The method of in an earlier section.

is dependent on the particle size other intrinsic solubilities, compared by explained by the existence of a particles, resulting in a thermody- ted by greater dissolution of the ed solution. The increase in intrin- ce, however, ceases when the par- further decrease in particle size

d by the pH of the liquid medium ple, a weakly acidic drug is more weakly basic drug is more soluble is due to the formation of more ion. Conversely, the weakly acidic the pH is lowered by the addition will precipitate from the solution alkali. The precipitation is a result to the less soluble nonionized form. ility of material is given by Eqs. modified from the Henderson- imation of the solubility of mate-

$$\frac{S - S_0}{S_0} \quad (5)$$

$$\frac{S_0}{S - S_0} \quad (6)$$

rug and  $S_0$  is the solubility of its

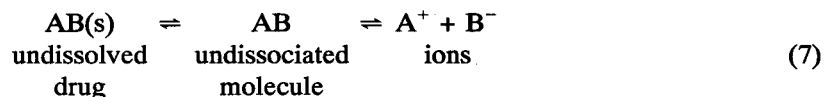
porated into the solvent in which solution may exist as ionized or in the solvent to form ions are de-

scribed as ionizable, whereas those that do not dissociate are nonionizable. Similar to the drugs, some additives ionize readily in the solvent, whereas others do not. Among the additives that ionize, some produce an ion similar to the drug. The effects of additives on the solubility of a drug depend on the nature of the drug as well as the additives. For ease of understanding, the additives will be classified as common ions, indifferent electrolytes, and nonelectrolytes.

### 1. *Effect of Common Ions on the Solubility of Ionizable Drugs*

The solubility of a sparingly soluble drug is decreased by an additive that possesses an ion similar to the drug. This phenomenon, which is a result of the common ion effect, can be explained by the law of mass action.

The equilibrium of a saturated solution in the presence of undissolved drug is represented as follows:



If the material is sparingly soluble, the concentration of dissolved drug is sufficiently small to assume complete dissociation into ions. The overall equilibrium, therefore, may be expressed as



From the law of mass action, the equilibrium constant  $K$  for this reversible reaction is given by the following equation:

$$K = \frac{[\text{A}^+][\text{B}^-]}{[\text{AB(s)}]} \quad (9)$$

where the square brackets indicate the concentrations of the respective components. Because the concentration of a solid may be considered to be constant, Eq. (9) can be rewritten as

$$K'_s = [\text{A}^+][\text{B}^-] \quad (10)$$

where  $K'_s$  is a constant known as the *solubility product* of the drug AB. Some drugs have molecules that contain more than one ion of each type. The equilibrium and solubility product of these drugs are similarly expressed as



$$K'_s = [\text{A}^+]^x[\text{B}^-]^y \quad (12)$$

If the additive dissociates to produce either  $A^+$  or  $B^-$ , the concentrations of these ions in the solvent will increase. As a result, the product  $[A^+][B^-]$  or  $[A^+][B^-]^y$  will also increase. It should be recalled that  $K'_S$  is a constant. Therefore, if  $K'_S$  is exceeded by the product of the concentrations of ions, the equilibrium will move toward the left to restore the equilibrium, and the drug will be precipitated. This explains the decrease in the solubility of a drug by the common ion effect.

## 2. Effect of Indifferent Electrolytes on the Solubility of Ionizable Drugs

Additives that dissociate to form ions different from those of the drug are known as *indifferent electrolytes*. Unlike common ions, indifferent electrolytes may increase the solubility of a sparingly soluble drug.

The solubility product defined by Eq. (10) is only an approximation from the more exact thermodynamic relation expressed by the following equation:

$$K_S = (\alpha_{A^+})(\alpha_{B^-}) \quad (13)$$

where  $K_S$  is the solubility product of drug AB and  $\alpha_{A^+}$  and  $\alpha_{B^-}$  are the activities of the respective ions. The *activity of an ion* is defined as the effective concentration of the ion in solution. It generally has a lower value than the actual concentration because some of the ions are "taken out of play" by strong association with oppositely charged ions.

At infinite dilution, the wide separation of ions prevents interionic association, and the actual concentration and activity of the ion are equal. This situation is applicable to a sparingly soluble drug for which the concentrations of ions produced are so small that the ions are completely unassociated. Therefore, the solubility product can be expressed by Eq. (10). However, if the concentration of ions increases, the effects of interionic association are no longer negligible and the activity becomes less than the actual concentration. The activity coefficient, which is the ratio of activity to actual concentration [Eq. (14)] indicates the extent of interionic association. An activity coefficient of unity shows that the ions are completely unassociated, whereas smaller values show greater interionic association.

$$\frac{\alpha_{A^+}}{[A^+]} = f_{A^+} \quad \text{or} \quad \alpha_{A^+} = f_{A^+}[A^+] \quad (14)$$

where  $f_{A^+}$  is the activity coefficient of ion A.

Equation 13 can thus be expressed as

$$K_S = f_{A^+} \cdot [A^+] \cdot f_{B^-} \cdot [B^-] = f_{A^+} \cdot f_{B^-} \cdot [A^+] \cdot [B^-] \quad (15)$$

According to Eq. (10), the product of the activities  $\alpha_{A^+}\alpha_{B^-}$  is equated to  $f_{A^+}f_{B^-}$  where  $f_{A^+}f_{B^-}$  is the product of the activity coefficients. Hence,

$$K_S = K'_S f_{A^+} f_{B^-}$$

The value of the activity coefficients  $f_{A^+}$  and  $f_{B^-}$  depends on the concentration of ions of the solvent. It follows that  $K'_S$  will increase with increasing concentration of indifferent electrolytes. The increase in the solubility of a drug by indifferent electrolytes is attributed to the decrease in the activity coefficients of the ions owing to the indifferent electrolyte effect.

## 3. Effect of Nonelectrolytes on the Solubility of Ionizable Drugs

The solubility of an ionizable drug is affected by the addition of nonelectrolytes into the solvent. The degree of dissociation of the drug into ions is reduced in the solvent. Solvents with a high dielectric constant tend to reduce the forces that attract the ions, thus promoting the dissociation of the drug. Addition of nonelectrolytes lowers the dielectric constant of the solvent, thus reducing the dissociation and, subsequently, the solubility of the drug.

## 4. Effect of Electrolytes on the Solubility of Nonionizable Drugs

Nonionizable drugs do not dissociate into ions. They exist as single molecules, and their solubility is determined by the formation of weak intermolecular bonds between the drug and the solvent. For example, the solubility of a drug in water is increased by the formation of hydrogen bonds between the drug and the water molecules. If an electrolyte is added, it will displace the drug from the water molecules, thus reducing the solubility of the drug for water. These ions will compete with the drug for water and reduce the solubility of the drug.

## 5. Effect of Surfactants on the Solubility of Drugs

Surfactants are solutes that can reduce the surface tension of the solvent. These substances are used in pharmaceuticals for wetting, and emulsifying agents. A drug that has little affinity for water will be more soluble in a solution that has little affinity for water. At a specific concentration, the surfactant will form a micelle, and the drug will be solubilized in the micelle.

either  $A^+$  or  $B^-$ , the concentration increases. As a result, the product  $K'_S$  should be recalled that  $K'_S$  is the product of the concentrations of the ions to the left to restore the equilibrium, and  $K_S$  maintains the decrease in the solubility

### the Solubility of

different from those of the drug are common ions, indifferent electrolytes, and a highly soluble drug.

Eq. (10) is only an approximation of the activity expressed by the following

(13)

Drug AB and  $\alpha_{A^+}$  and  $\alpha_{B^-}$  are the activity of an ion is defined as the activity of the ion. It generally has a lower value than the activity of the ions are "taken out of the solution" by charged ions.

The activity of ions prevents interionic association and activity of the ion are equal. For a highly soluble drug for which the concentration of the ions are completely unassociated, the effect can be expressed by Eq. (10). As the concentration increases, the effects of interionic association become less than the effect of the solvent, which is the ratio of activity of the ion to the activity of the drug. This shows the extent of interionic association. It shows that the ions are completely unassociated by greater interionic association.

(14)

A.  
s

$[A^+][B^-]$

(15)

According to Eq. (10), the product of the concentrations is the constant  $K'_S$ . The product of the activity coefficients of the respective ions may be equated to  $f_{A^+B^-}^2$  where  $f_{A^+B^-}$  is the mean activity coefficient of the drug. Hence,

$$K_S = K'_S f_{A^+B^-}^2 \quad (16)$$

The value of the activity coefficient decreases from unity as the overall concentration of ions of the solution increases. Because  $K_S$  is a constant, it follows that  $K'_S$  will increase with the ionic strength and become larger than  $K_S$ . The increase in the solubility of a drug by the addition of indifferent electrolytes is attributed to the increase in the ionic strength of the solution owing to the indifferent electrolytes.

### 3. Effect of Nonelectrolytes on the Solubility of Ionizable Drugs

The solubility of an ionizable drug depends on the dissociation of the drug into ions. The degree of dissociation is affected by the dielectric constant of the solvent. Solvents with a high dielectric constant, being polar, are able to reduce the forces that attract the oppositely charged ions produced by dissociation of the drug. Addition of a nonelectrolyte, such as alcohol, will lower the dielectric constant of the solvent. This will decrease the dissociation and, subsequently, the solubility of the drug.

### 4. Effect of Electrolytes on the Solubility of Nonionizable Drugs

Nonionizable drugs do not dissociate into ions in solution. They exist as single molecules, and their solubilities in the solvent depend on the formation of weak intermolecular bonds with the molecules of the solvent. For example, the solubility of the drug in water is dependent on the formation of hydrogen bonds between the molecules of the drug and water. When an electrolyte is added, it will dissociate to form ions that have a high affinity for water. These ions will compete with the molecules of the drug for water and reduce the solubility of the drug in water.

### 5. Effect of Surfactants

Surfactants are solutes that cause a marked decrease in the surface tension of the solvent. These substances are commonly employed as solubilizing, wetting, and emulsifying agents. They are composed of a lipophilic group that has little affinity for water and a hydrophilic group that has strong affinity for water. At a specific concentration, known as the critical micellar

concentration (CMC), the surfactant molecules exist as large aggregates called micelles. In an aqueous system, the hydrophilic groups are orientated on the exterior, whereas the lipophilic groups are on the interior of the micelles. Drugs that are poorly soluble in water may be taken into the interior of these micelles, resulting in more drug being able to go into solution. The enhanced solubility obtained as a result of the solubilization phenomenon is known as the *apparent solubility* of the drug.

## 6. Effect of Complex Formation

The amount of drug that can go into solution may be altered by the addition of a substance that interacts with the drug to form a complex. The solubility of the complex will determine the apparent solubility of the drug. If the complex is more soluble than the drug, a larger amount of the drug will dissolve to form the complex. Thus, the drug will show a higher solubility in the solvent. Similarly, if the complex is less soluble, some of the drug will be precipitated in the form of the complex. Therefore, the drug will show a lower solubility in the solvent. It should be remembered that the modified solubility obtained is not the solubility, but is the apparent solubility of the drug.

## IV. CRYSTAL PROPERTIES AND POLYMORPHISM

Materials may occur as amorphous substances without any definite structure, or as crystalline particles with a definite structure and shape. Some materials may exist in more than one crystalline form (polymorph) and are described as exhibiting polymorphism. The type of crystal formed depends on the conditions, such as temperature and type of solvent, under which crystallization is induced. At a specific temperature or pressure, more than one polymorph can exist, but only one will be thermodynamically stable. The less stable or metastable forms will be converted to the stable form with time. Studies show that it may take from minutes to years to revert to the stable lattice structure.

The different crystalline forms of a material generally differ in many physical characteristics, such as solubility, melting point, optical and electrical properties, density, hardness, and stability. The use of metastable polymorphs frequently results in higher solubility and dissolution rates, whereas the stable polymorphs are often more resistant to chemical degradation. It is obvious that any change in the crystalline form will affect the therapeutic efficacy of a pharmaceutical product. Therefore, in the formulation of pharmaceutical products, a knowledge of the crystalline form of a drug is very

important, and steps should be taken to prevent the drug from reverting from one form to another. Some problems that may arise with polymorphs that are not properly characterized are the stability of drug. The significance of this is discussed in detail [17].

Various techniques may be used to identify the material. It is advisable to employ more than one method for the use of only one method.

## A. Dissolution Study

An amount of the material is placed in a dissolution medium, and aliquot samples are withdrawn at regular time intervals. The concentration of the drug in the medium is then plotted. The curve obtained is reflected by the shape of the dissolution profile. The shape of the curve of a metastable polymorph that is converted to the stable form is shown in Fig. 5a. The concentration of the drug in the medium drops much more rapidly at the initial stage than that of the stable polymorph. The dissolution profile just gradually increases. The metastable form is indicated by the curve. The dissolution curve of such a polymorph, indicating that the form is converted to the stable form, of each curve indicates the sol-

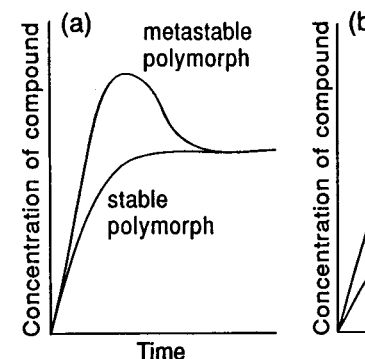


Fig. 5 Typical dissolution profiles.

olecules exist as large aggregates hydrophilic groups are orientated groups are on the interior of the water may be taken into the in-ug being able to go into solution. ult of the solubilization phenom- f the drug.

n may be altered by the addition o form a complex. The solubility nt solubility of the drug. If the larger amount of the drug will ug will show a higher solubility less soluble, some of the drug mplex. Therefore, the drug will should be remembered that the ability, but is the apparent solu-

## POLYMORPHISM

es without any definite structure, cture and shape. Some materials a (polymorph) and are described crystal formed depends on the f solvent, under which crystalli- or pressure, more than one pol- rmodynamically stable. The less ed to the stable form with time. s to years to revert to the stable

material generally differ in many melting point, optical and elec- ility. The use of metastable pol- ty and dissolution rates, whereas tant to chemical degradation. It f form will affect the therapeutic fore, in the formulation of phar- ystalline form of a drug is very

important, and steps should be taken to ensure that the crystals do not convert from one form to another during production and storage of the product. Some problems that may arise if the crystal properties of the drug are not properly characterized are precipitation, low stability, and poor bioavailability of drug. The significance of polymorphism in pharmacy has been discussed in detail [17].

Various techniques may be used to identify the crystalline form of a material. It is advisable to employ more than one method in the analysis, for the use of only one method is sometimes unreliable.

### A. Dissolution Study

An amount of the material in excess of its solubility is added to the dissolution medium, and aliquot samples are removed and assayed at appropriate time intervals. The concentration of the material in solution as a function of time is then plotted. The crystalline form that constitutes the material is reflected by the shape of the dissolution curve. The typical dissolution profile of metastable polymorph that readily reverts to the stable form is shown in Fig. 5a. The concentration of the metastable polymorph is noted to increase much more rapidly at the initial period of the dissolution study and then drops to that of the stable polymorph. For the stable polymorph, the dissolution profile just gradually increases to a plateau. The solubility of the metastable form is indicated by the peak of its dissolution curve. Occasionally, the metastable polymorph does not revert readily to the stable form. The dissolution curve of such a metastable form lies above that of the stable form, indicating that the former is more soluble (see Fig. 5b). The plateau of each curve indicates the solubility of the respective polymorph.

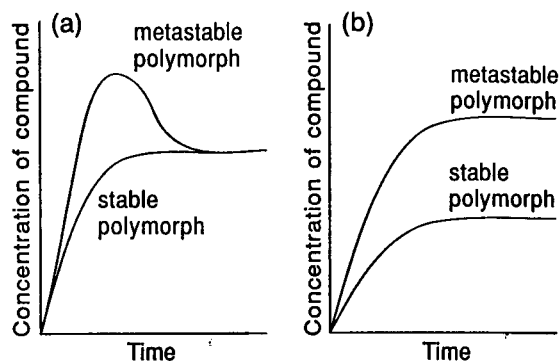


Fig. 5 Typical dissolution profiles.



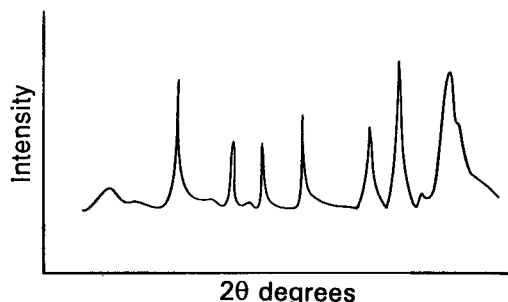


Fig. 6 Typical X-ray diffractogram.

### B. X-Ray Diffraction

Crystalline materials in powder form exhibit characteristic X-ray diffraction patterns, with peaks of varying heights and in different positions. These diffraction patterns are also known as X-ray diffractograms. A typical X-ray diffractogram is illustrated in Fig. 6.

The polymorphs of a material have different crystal-packing arrangements and thus produce differences in their diffractograms, from which the crystalline form of the material is identified. This method of analysis is nondestructive and requires a very small sample of the material, which can be examined without further processing. X-ray diffraction studies are especially useful for investigations on the changes of crystalline form during processing. Occasionally, the extent of the conversion of a crystalline drug to the amorphous form can be determined.

### C. Infrared Analysis

The polymorphs of a material show varying crystal-packing arrangements and produce different X-ray diffractograms. The crystal-packing arrangement also affects the energy of molecular bonds and results in different infrared spectra for the polymorphs of a material. Identification of the crystalline form of a material is based on the spectrum derived. Infrared analysis can be used for both qualitative and quantitative identification. It is important to use only materials in the solid form, because the polymorphs of a material in solution have identical infrared spectra.

### D. Thermal Analysis

In this method, the polymorphs are identified by their thermal behaviors. The change in energy of the polymorph as it undergoes transformation when

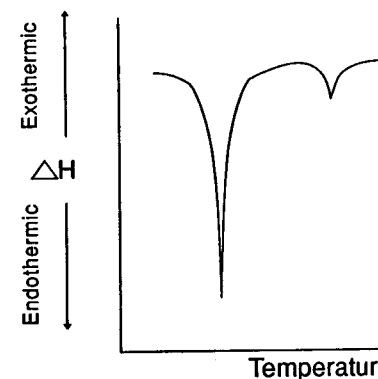


Fig. 7 Example of a thermogram.

it is heated is recorded as a thermogram, as given in Fig. 7. The thermogram peaks pointing downward indicate endothermic processes such as melting and desolvation. The different thermograms, which are characteristic of different polymorphs, can be used to identify the different polymorphs.

Differential-scanning calorimetry (DSC) is one of two methods of thermal analysis. In DSC, the heat flow during a transformation is recorded as a function of temperature (the energy is expressed as heat flow versus inert substance).

### E. Hot-Stage Microscopy

The polarizing microscope fitted with a hot-stage is used for studying the crystalline forms of a material. The material is heated to a temperature at which a transformation in appearance that is characteristic of a polymorph occurs.

## V. OTHER PHYSICAL PROPERTIES

It is undoubted that the type of physical property of an excipient depends very much on the processing involved. Material testing, which includes, namely, physical testing and functional testing, is used to determine properties

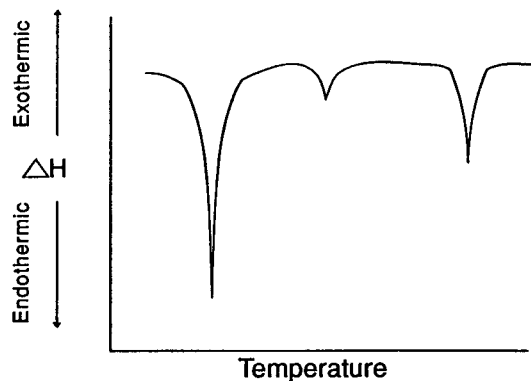


Fig. 7 Example of a thermogram.

hibit characteristic X-ray diffraction and in different positions. These ray diffractograms. A typical X-ray

different crystal-packing arrangements, from which the diffractograms, from which the sample of the material, which can X-ray diffraction studies are especially changes of crystalline form during the conversion of a crystalline drug

ing crystal-packing arrangements. The crystal-packing arrangements and results in different infrared spectrum derived. Infrared analysis is important for identification. It is important to identify the polymorphs of a material

fied by their thermal behaviors. It undergoes transformation when

it is heated is recorded as a thermogram. An example of a thermogram is given in Fig. 7. The thermogram consists of characteristic peaks. The peaks pointing downward indicate endothermic changes, such as melting, sublimation and desolvation. The different polymorphs of a material will exhibit different thermograms, which allow them to be identified.

Differential-scanning calorimetry and differential thermal analysis are two methods of thermal analysis commonly used for these studies. In differential-scanning calorimetry, the energy resulting from the crystalline transformation is recorded as a function of temperature. In differential thermal analysis, the energy is expressed by differential temperature (sample versus inert substance).

### E. Hot-Stage Microscopy

The polarizing microscope fitted with a hot stage is very useful for identifying the crystalline forms of a material. In this method, the polymorph is heated to a temperature at which it undergoes a change in birefringence or appearance that is characteristic of the polymorph.

## V. OTHER PHYSICAL PROPERTIES

It is undoubted that the type of physical characterization tests for a drug or excipient depends very much on the material concerned as well as the processing involved. Material testing can be broadly divided into two types: namely, physical testing and functionality testing. Physical testing, which is used to determine properties such as size, solubility, and crystal form, is



are better established. Functions such as lubricity, flow, creep, and tack, may yield useful information about effects on the processing.

A helium pycnometer, true densities increase and at a high degree of accuracy the formulator the identity of type of raw materials, such as partially hydrated form.

It reveals its rheological properties. A volumetrically calibrated cylinder weight of powder filled and the change, changes in apparent densities flowability [18]. A small change in density indicates good flow properties. The difference between poured density to poured density—is expressed. The *poured density* is the undisturbed density of a calibrated cylinder after filling, and the *tapped density* is the density of the powder until no change in the packing density is observed. The *tapped density* is used to predict powder flowability which is the ratio of the difference between the poured density and the tapped density, expressed as

It is determined directly using a flowmeter by the angle of repose. Angle of repose is determined by forming a conical powder heap and measuring the angle of the heap. Powders that can flow well will have a low angle of the heap-forming measurement. A transparent cylinder partially filled with powder is bedded away from the initial horizontal position. The angle of inclination when sliding the cylinder will increase the powder flowability. Shear tests are carried out to evaluate the cohesiveness of shear cells for evaluation of

Tests of powders under pressure are also carried out. This study can be made using force transducers [20]. The force exerted is used to calculate useful parameters for powder mix.

For polymers, mechanical testing, such as creep testing of films formed, can provide information on the suitability of the polymer or the additives added for their film-forming function [21]. When polymers are used as a binder, adhesive properties in addition to polymer viscosity may be determined. The adhesive property can be evaluated by the measurement of tack or stickiness. This measurement involves determining the force required to detach two platens held together by the polymer solution. Other tests that may be carried out include measurements for surface activity, glass transition temperature, cloud point, and adhesion strength of dried polymer.

## VI. COMMONLY USED EXCIPIENTS IN GRANULATION

Excipients for granulation can be largely divided into two categories: bulking agents and functional additives. It is true that bulking agents or fillers also serve a function in that they form the core or structure of a dosage form. Nevertheless, bulking agents generally differ from the functional additives in that they are usually inert materials that are relatively inexpensive. Functional additives include binders, disintegrants, lubricants, colorants, and stabilizing agents. Besides the pharmacopeia, several recently published handbooks can provide a compilation of commonly used pharmaceutical excipients [22,23].

The choice of excipients depends on several factors; namely, the drug used, the process involved, the formulator, and the cost of excipient. Differences will be seen in the choice of excipients by innovator companies and generic companies, because they have different cost considerations. Some granulation processes, such as fluid bed granulation, would require tighter control of drug and excipient specifications, compared with wet granulation using a paddle mixer. In fluid bed, besides the control of particle size distribution, the excipient's particle density should not be too greatly different from that of the drug. Extrusion-spheronization would generally require microcrystalline cellulose.

A very common filler is lactose, although other sugars, dicalcium phosphate, starch, pregelatinized starch, and microcrystalline cellulose are also used. The starches and microcrystalline cellulose are also disintegrants in tablets. For tablets, other commonly used disintegrants include sodium starch glycolate, croscarmellose, crospovidone, and low-substituted hydroxypropylcellulose. Lubricants are usually not added until just before filling or tableting of the granules. The most commonly used lubricant is magnesium stearate. Other lubricants used include calcium stearate, stearic acid, wax, hydrogenated vegetable oil, talc, and starch. Much work has been done on lubricants, and it is well established that the physical characterization of the



istency in functionality, especially 4].

of a wide variety of sugars and synthetic. Sugars used include natural polymers are acacia, alginic. There is an inherent variability in and this sometimes gives rise to characterize binders for their vis- potential processing problems. The use, sodium carboxymethylcellu- lose, and hydroxypropylmethyl- al binders, variability between the same supplier can be expected several viscosity grades are avail- use are polyvinylpyrrolidone and is widely used in both wet mass- plication of polyethylene glycol

aceutical products include color- , and release rate modifiers. They are specific characterization tests. nts to be added must be carefully is bioavailable and aesthetically dergo a processing schedule for product, it is likely that the pro- w materials have not been stan-

## EXCIPIENT

product, it is imperative to ensure with one another. Incompatibilities well as between the excipients tested through many modes, such ation, resulting in lower potency c efficacy of the product. There- , and this is achieved by carrying between the components used in

## A. Stability Study

A stability study is the traditional method of detecting incompatibilities. Mixtures of the drug and excipient are prepared and stored under exaggerated conditions of heat, light, and humidity. A detailed discussion on the "realistic" proportions of drug and excipient to be used in the investigation is given by Akers [25]. The mixtures are examined for any physical change and aliquot samples are withdrawn for assay of the intact drug at varying time intervals. Incompatibility is reflected by various signs such as appearance of precipitate and decrease in the concentration of intact drug.

## B. Thermal Analysis

A relatively simple approach for the investigation of potential interaction between a drug and an excipient can be carried out using differential-scanning calorimetry. The drug, individual excipients, and binary mixtures of the drug and excipient are separately scanned at a standard rate over a temperature range that encompasses all the thermal features of the drug and excipients. Each mixture consists of 50% drug and excipient, respectively, to maximize the likelihood of an interaction. The thermograms of the mixtures and the appropriate individual components are compared. Interaction is deduced by changes in the thermal features, such as the elimination of or the appearance of a peak in the thermogram of the mixture. This is illustrated in Fig. 8. Changes in shape, onset, maximum temperature, and relative height of the peaks may also indicate interaction. However, it should be cautioned that these changes could also arise from physical mixing of the components.

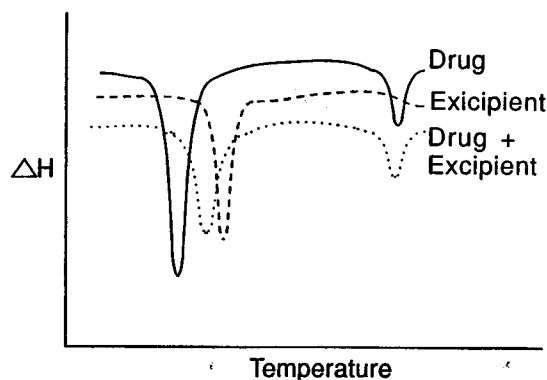


Fig. 8 Thermograms indicating drug-excipient interaction.

A big advantage of differential-scanning calorimetry over the traditional stability test is the speed of determination. However, similar to all methods, differential-scanning calorimetry has its own limitations. It is not applicable if the test materials exhibit properties that make data interpretation difficult, such as eutectic formation, coincident melting, and dissolution of one component in the melt of the other. It is not advisable to rely on differential-scanning calorimetry alone to determine incompatibility. Chrzanowski et al. [26] reported that differential-scanning calorimetry indicated no incompatibilities in mixtures of fenretinide-excipient and mefenidil-excipient, whereas the traditional stability study showed some incompatibilities. Hence, differential-scanning calorimetry should be used only to supplement the stability test by eliminating the incompatible excipients and reducing the number of the test samples.

### C. Chromatographic Methods

Chromatography was first used for the separation of colored leaf pigments. The operation of chromatography is based on the distribution of a material between a stationary phase and a mobile phase. The stationary phase can be a solid or a liquid supported on a solid, and the mobile phase can be a gas or a liquid that flows continuously around the stationary phase. The different components in a mixture can be separated and identified as a result of differences in their affinity for the stationary phase.

In addition to its application in the separation and identification of materials, chromatography is also employed to detect potential interactions between materials. Both thin-layer chromatography and liquid chromatography are commonly employed in this area of study. In thin-layer chromatography, the stationary phase consists of a powder adhered onto a glass, plastic, or metal plate. The powders commonly used are silica, alumina, polyamides, cellulose, and ion-exchange resins. Solutions of the drug, excipient and drug-excipient mixture are prepared and spotted on the same baseline at one end of the plate. The plate is then placed upright in a closed chamber containing the solvent, which constitutes the mobile phase. As the solvent moves up the plate, it carries with it the materials. Those materials that have a stronger affinity for the stationary phase will move at the slower rate. The material is identified by its  $R_f$  value, which is defined as the ratio of the distance the material has moved to the distance the solvent front has moved. The position of the material on the plate is indicated by spraying the plate with certain reagents or exposing the plate to ultraviolet radiation. If there is no interaction between the drug and excipient, the mixture will produce two spots the  $R_f$  values of which are identical with those of the individual drug and excipient. If there is interaction, the complex formed

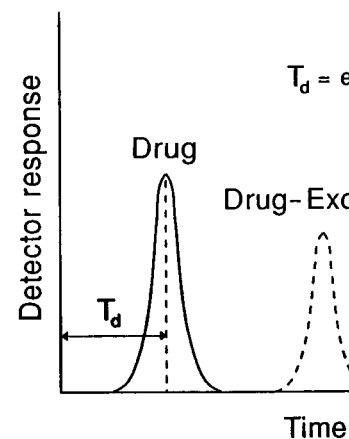


Fig. 9 Chromatograms illustrating the separation of Drug and Drug-Excipient mixture.

will produce a spot the  $R_f$  value of which is different from those of the individual components.

In liquid chromatography, a solid stationary phase in a column is used. The material is identified by its  $R_f$  value. Solutions of the drug, excipient and drug-excipient mixture are prepared and injected into the column. The components move at different speeds, depending on their interaction with the stationary phase. The time of the material that elutes from the column is measured against time to give a chromatogram. If there is no interaction between the drug and excipient, the complex formed will produce two spots the  $R_f$  values of which are identical with those of the individual components. If there is interaction, the complex formed will produce a spot the  $R_f$  value of which is different from those of the individual components. The chromatograms of the drug, excipient and drug-excipient mixture are compared together. Similarly, gas chromatography can be used to detect potential interactions between materials.

## VIII. SUMMARY

The greatest difficulty for the identification of material character and extent of material character is the lack of effective in the long run. Often, the identification necessitates further material character study to solve the problem or to prevent the identification of the more common material. The identification carried out and the potential

ning calorimetry over the tradi-  
 mination. However, similar to all  
 has its own limitations. It is not  
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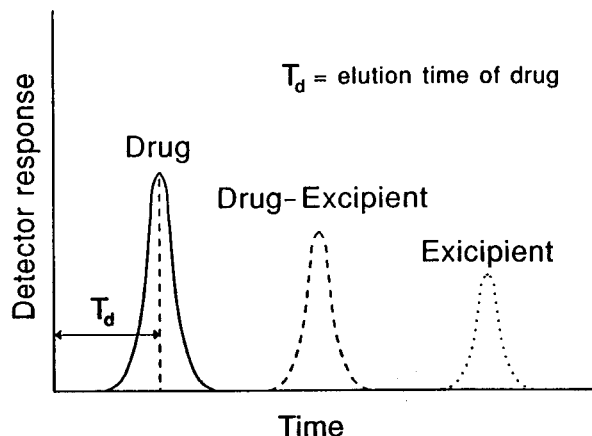


Fig. 9 Chromatograms illustrating drug-excipient interaction.

will produce a spot the  $R_f$  value of which is different from those of the individual components.

In liquid chromatography, the distribution of the material between the solid stationary phase in a column and the liquid mobile phase is determined. The material is identified by the time taken for it to elute from the column. Solutions of the drug, excipient, and drug-excipient mixture are prepared and injected into the column. The materials will elute from the column at different speeds, depending on their affinity for the column. The concentration of the material that elutes from the column is detected and plotted against time to give a chromatogram. If there is interaction between the drug and excipient, the complex formed will exhibit an elution time different from those of the individual components. This is illustrated in Fig. 9, which shows the chromatograms of the drug, excipient, and drug-excipient mixture plotted together. Similarly, gas chromatography may be used.

## VIII. SUMMARY

The greatest difficulty for any process technologist is to decide on the type and extent of material characterization to be undertaken such that it is cost-effective in the long run. Often, it is a problem from the production run that necessitates further material characterization to be carried out, either to resolve the problem or to prevent future occurrences. This chapter serves to identify the more common material characterization methods that can be carried out and the potentially useful information that can be inferred from



the tests. It is hoped that the discussion of the many methods of material characterization could help in the choice of characterization methods for material testing.

## REFERENCES

1. H Heywood. The evaluation of powders. *J Pharm Pharmacol Suppl* 15:56T, 1963.
2. H Wadell. Volume, shape and roundness of rock particles. *J Geol* 40:443, 1932.
3. NG Stanley-Wood. Particle characterisation by size, shape and surface for individual particles. In: NG Stanley-Wood, ed. *Enlargement and Compaction of Particulate Solids*. London: Butterworths, 1983, p. 18.
4. BH Kaye. Multifractal description of ragged fine particle profile. *Particle Char* 1:14, 1984.
5. BH Kaye. Specification on the ruggedness and/or texture of a fine powder profile by its fractal dimension. *Powder Technol* 21:1, 1978.
6. AG Flook. The use of dilation logic on the Quantimet to achieve dimension characterisation of textured and structured profiles. *Powder Technol* 21:295, 1978.
7. P Meakin. Simulations of aggregation process. In: D. Avnir, ed. *The Fractal Approach to Heterogeneous Chemistry*. Chichester: John Wiley & Sons, 1990.
8. T Allen. *Particle Size Measurement*. 4th ed. London: Chapman & Hall, 1990.
9. L Svarosky. Characterization of powders. In: MJ Rhodes, ed. *Principles of Powder Technology*. Chichester: John Wiley & Sons, 1990, p. 35.
10. C Washington. *Particle Size Analysis in Pharmaceuticals and Other Industries*. Chichester: Ellis Horwood, 1992.
11. British Standard 3406, Part 4, 1963.
12. V Timbrell. A method of measuring and grading microscopic spherical particles. *Nature* 170:318, 1952.
13. JC Russ. *Computer-Assisted Microscopy*. New York: Plenum Press, 1990.
14. KSW Sing. Adsorption methods for surface area determinations. In: NG Stanley-Wood, RW Lines, eds. *Particle Size Analysis*. Cambridge: The Royal Society of Chemistry, 1992, p. 13.
15. S Lowell, JE Shields. *Particle Surface Area and Porosity*. 2nd ed. London: Chapman & Hall, 1983, p. 205.
16. HE Buckley. *Crystal Growth*. New York: John Wiley & Sons, 1951, p. 29.
17. J Haleblian, W McCrone. Pharmaceutical applications of polymorphism. *J Pharm Sci* 58:911, 1969.
18. M Yamashiro, Y Yuasa, K Kawakita. An experimental study on the relationships between compressibility, fluidity and cohesion of powder solids at small tapping numbers. *Powder Technol* 34:225, 1983.
19. MC Kostelnik, JC Beddow. New techniques for tap density in modern developments in powder metallurgy. In: HH Hausner, ed. *Processes*. New York: Plenum Press, 1970.
20. PR Watt. *Tablet Machine Practice*. Chichester: Ellis Horwood, 1990.
21. AO Okhamfae, P York. Interfacial and testing methods. *Int J Pharm* 11:1, 1976.
22. *Handbook of Pharmaceutical Technology*. Washington DC, and London: Taylor & Francis, 1986.
23. HG Brittain, ed. *Analytical Pharmaceutical Technology*. San Diego: Academic Press, 1990.
24. ZT Chowhan. Excipients and their use. *Pharm Technol* 17:72, 1993.
25. MJ Akers. Preformulation testing. *Pharm Technol* 11:1, 1976.
26. FA Chrzanowski, LA Ullissi. Compatibility testing. Application versus a wet granulation system. *Pharm* 12:703, 1986.

of the many methods of material  
e of characterization methods for

s. J Pharm Pharmacol Suppl 15:56T,

of rock particles. J Geol 40:443, 1932.  
ion by size, shape and surface for in-  
, ed. Enlargement and Compaction of  
, 1983, p. 18.

ged fine particle profile. Particle Char

ness and/or texture of a fine powder  
Technol 21:1, 1978.

the Quantimet to achieve dimension  
ed profiles. Powder Technol 21:295,

rocess. In: D. Avnir, ed. The Fractal  
Chichester: John Wiley & Sons, 1990.  
ed. London: Chapman & Hall, 1990.  
s. In: MJ Rhodes, ed. Principles of  
iley & Sons, 1990, p. 35.

Pharmaceutics and Other Industries.

grading microscopic spherical parti-

New York: Plenum Press, 1990.  
urface area determinations. In: NG  
ize Analysis. Cambridge: The Royal

Area and Porosity. 2nd ed. London:

John Wiley & Sons, 1951, p. 29.  
al applications of polymorphism. J

experimental study on the relation-  
d cohesion of powder solids at small  
, 1983.

ues for tap density in modern devel-  
Hausner, ed. Processes. New York:

20. PR Watt, Tablet Machine Instrumentation in Pharmaceutics: Principles and Practice. Chichester: Ellis Horwood, 1988.
21. AO Okhamfae, P York. Interaction phenomena in pharmaceutical film coatings and testing methods. Int J Pharm 39:1, 1987.
22. Handbook of Pharmaceutical Excipients. American Pharmaceutical Association, Washington DC, and Pharmaceutical Society of Great Britain, London, 1986.
23. HG Brittain, ed. Analytical Profiles of Drug Substances and Excipients. San Diego: Academic Press, 1993.
24. ZT Chowhan. Excipients and their functionality in drug product development. Pharm Technol 17:72, 1993.
25. MJ Akers. Preformulation testing of solid oral dosage form drugs. Can J Pharm 11:1, 1976.
26. FA Chrzanowski, LA Ulissi, BJ Fegely, AC Newman. Preformulation excipient compatibility testing. Application of differential scanning calorimetric method versus a wet granulation simulating isothermal stress method. Drug Dev Ind Pharm 12:703, 1986.

# 4

## Binders and Solvents

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## I. INTRODUCTION

Binders are the adhesives that are added to the tablet formulations. The role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet. In a wet granulation process, binders promote size enlargement to provide granules and, thereby, improve flowability of the blend during the manufacturing process. Binders may also improve the hardness of the tablets by enhancing intragranular as well as intergranular forces. In a direct compression process, binders often act as fillers and impart compressibility to the powder blend. The cohesive properties of binders may reduce friability of the tablets and, thus, aid in their elegance. Although the purpose of using binders in a tablet formulation is not to influence its disintegration and dissolution rate, these properties may be modified owing to the altered wettability of the formulation.

## II. TYPES OF BINDERS

Binders are classified as natural polymers, synthetic polymers, or sugars. The selection of a binder for a particular system is mostly empirical and depends on the previous experience of the formulator. Selection of the quantity of binder required in a particular system can be determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration time, and the drug dissolution rate. Some commonly used binders in wet granulation, with their usual concentration range along with the granulating system, are listed in Table 1.

The basic properties of some widely used binders, with their method of incorporation, will be discussed in this section [1-4].

### A. Natural Polymers

#### 1. Starch

Starch is a polymeric carbohydrate obtained from various plant sources, such as potato, wheat, maize, rice, and tapioca. It is generally regarded as safe (GRAS)-listed material and one of the most widely used tablet binders. It is insoluble in cold water and in alcohol, but it gelatinizes (hydrolyzes) in hot water to form a paste. Starch paste can be prepared by dispersing starch in 1-1.5 parts of cold water for initial wetting, followed by addition of 2 to 4 times as much boiling water, with continuous stirring, until a translucent paste is obtained. This is further diluted by cold water to the desired concentration. Alternatively, starch paste can also be prepared by heating the

## Binders and Solvents

**Table 1** Commonly Used Granulating Systems

Binder	Method of incorporation
<b>Natural polymers</b>	
Starch	Wet method
Pregelatinized starch	Wet method
	Dry method
Gelatin	Wet method
Acacia	Wet method
Alginic acid	Dry method
Sodium alginate	Wet method
<b>Synthetic polymers</b>	
Polyvinylpyrrolidone	Wet method
	Dry method
Methylcellulose	Wet method
	Dry method
HPMC	Wet method
	Dry method
Na-CMC	Wet method
	Dry method
Ethylcellulose	Wet method
	Dry method
<b>Sugars</b>	
Glucose	Wet method
Sucrose	Wet method
Sorbitol	Wet method

Source: Ref. 3.

cold water suspension of starch with constant stirring.

Freshly prepared starch paste is used w/w in a tablet granulation. Starch paste is produced when starch paste is used in a tablet formulation that disintegrate readily. During the granulation process, the high viscosity of the starch paste makes it difficult to incorporate into the powder blend.

**Table 1** Commonly Used Granulating Systems

Binder	Method of incorporation	% used in formula	Solvent	% used in granulating system
<b>Natural polymers</b>				
Starch	Wet mixing	2-5	Water	5-25
Pregelatinized starch	Wet mixing	2-5	Water	10-15
	Dry mixing	5-10	Water	
Gelatin	Wet mixing	1-3	Water	5-10
Acacia	Wet mixing	3-5	Water	10-15
Alginic acid	Dry mixing	1-5	Water	
Sodium alginate	Wet mixing	1-3	Water	3-5
<b>Synthetic polymers</b>				
Polyvinylpyrrolidone	Wet mixing	0.5-5	Water or hydroalcoholic solution	5-10
Methylcellulose	Dry mixing	5-10		
	Wet mixing	1-5	Water	2-15
HPMC	Dry mixing	5-10		
	Wet mixing	2-5	Water or hydroalcoholic solution	5-10
Na-CMC	Dry mixing	5-10		
	Wet mixing	1-5	Water	5-15
Ethylcellulose	Dry mixing	5-10		
	Wet mixing	1-5	Ethanol	2-10
<b>Sugars</b>				
Glucose	Wet mixing	2-25	Water	25-50
Sucrose	Wet mixing	2-25	Water	50-67
Sorbitol	Wet mixing	2-10	Water	2-25

Source: Ref. 3.

to the tablet formulations. The role is essential for the bonding of the tablet. In a wet granulation process, binders provide granules and, thereby, enhance the manufacturing process. Binders enhance the intragranular adhesion during the compression process, binders often bind the powder blend. The cohesive properties of the tablets and, thus, aid in the granulation process. Binders in a tablet formulation enhance the dissolution rate, these properties enhance the stability of the formulation.

Binders, synthetic polymers, or sugars. The granulation system is mostly empirical and the selection of the granulator. Selection of the granulator can be determined by optimizing granule friability, tablet friability, and dissolution rate. Some commonly used granulation concentration range along with the granulation method is shown in Table 1.

used binders, with their method of granulation [1-4].

from various plant sources, such as starch. It is generally regarded as safe and is the most widely used tablet binders. It is prepared by dispersing starch in water, followed by addition of 2% water, followed by continuous stirring, until a translucent paste is formed. Cold water to the desired concentration can also be prepared by heating the

cold water suspension of starch to boiling in a steam-jacketed kettle with constant stirring.

Freshly prepared starch paste is used at a concentration of 5-25% w/w in a tablet granulation. Relatively soft and friable granules are produced when starch paste is used as a binder. Consequently, it yields tablets that disintegrate readily. During the wet-massing process, the high viscosity of the starch paste makes it difficult to evenly distribute the binder in the powder blend.

## 2. Pregelatinized Starch

Pregelatinized starch is a modified starch used in tablet formulations as a binder, diluent, and disintegrant. It is obtained by chemically and mechanically processing starch to rupture all or parts of the starch granules. This process renders starch granules flowable, and soluble in warm water without boiling. As a binder in a wet granulation process, pregelatinized starch can be used either as a solution reconstituted in water or by dry blending, followed by wetting with water. The latter process requires two to four times more binder to achieve the same binding effect.

Pregelatinized starch is available in fully or partially pregelatinized forms. The degree of pregelatinization determines its solubility in cold water. Cold water-soluble matter for a partially pregelatinized starch is 10–20%. Starch 1500 is partially pregelatinized starch containing 20% maximum cold water-soluble fraction, which makes it useful for wet granulation. The water-soluble fraction acts as a binder, whereas the remaining fraction facilitates the tablet disintegration process.

## 3. Gelatin

Gelatin is a mixture of purified protein fractions obtained by partial acid hydrolysis (type A gelatin) or alkali hydrolysis (type B gelatin) of animal collagens. It is insoluble in cold water and in alcohol, but is soluble in hot water. In hot water, gelatin forms a gel on cooling to 35–40°C. At temperatures higher than 40°C, the system exists as a solution. Therefore, the gelatin solutions must be used when warm to avoid gel formation.

During the preparation of gelatin solution, the gelatin must be wetted in cold water and then heated with gentle agitation to ensure dissolution. The agitation intensity must be controlled to prevent air entrapment in the viscous solution. Use of gelatin as a binder is limited in general-purpose tablets because it produces tablets characterized by high hardness and slow disintegration. However, these properties of gelatin, along with its smooth mouthfeel, can be advantageous in a lozenge formulation.

Gelatin reacts with aldehydes, aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, and surfactants. In a wet granulation process of a formulation containing color, the migration of dyes toward the upper surface of the static bed during the drying operation is often amplified by the presence of gelatin owing to its high affinity for dyes. The gelatin solutions are susceptible to microbial contamination on storage; therefore, freshly prepared solutions should always be used.

## Binders and Solvents

### 4. Acacia

Acacia, also named as gum arabic, is obtained from the sap of acacia trees. It is a complex, loose, and brittle substance, which is commercially available in a powdered form. As a tablet binder, it is used in dried form before moistening to prevent disintegration that disintegrate slowly. Acacia is resistant to enzymatic degradation. It is insoluble in water, ethanol, ferric salts, and with other synthetic polymers.

### 5. Tragacanth

Tragacanth is a naturally occurring gum, which is similar to those of acacia. Dry addition of tragacanth works better than addition in water when preparing the solution and the tablets.

### 6. Alginic Acid

Alginic acid is a polymannuronic acid, which acts as a binder and disintegrating agent. It slowly hydrolyzes at room temperature. It is best incorporated in a dry granulation process. It forms insoluble alginates with divalent and trivalent metals, with the exception of calcium. The disintegration of the tablets is delayed.

### 7. Sodium Alginate

Sodium alginate slowly dissolves in water. A 3–5% solution is used in wet granulation in sustained-release formulations to prevent drug from tablets. It is hygroscopic and susceptible to microbial contamination.

## B. Synthetic Polymers

### 1. Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) is a commonly used binder. It is

used in tablet formulations as a binder. It is obtained by chemically and mechanically modifying parts of the starch granules. This modified starch is not soluble in warm water without a heating process, pregelatinized starch can be dissolved in water or by dry blending, following a heating process requires two to four times the effect.

Partially or fully pregelatinized starch reduces its solubility in cold water. The amount of pregelatinized starch is 10–20%. Starch containing 20% maximum cold water-soluble starch is useful for wet granulation. The water-soluble fraction facilitates the remaining fraction facilitates

Fractions obtained by partial acid hydrolysis (type B gelatin) of animal skin are soluble in alcohol, but is soluble in hot water after cooling to 35–40°C. At temperatures above 40°C, it forms a solution. Therefore, the gelatin must be wetted to avoid gel formation.

In wet granulation, the gelatin must be wetted and agitated to ensure dissolution. To prevent air entrapment in the granules, the water is limited in general-purpose granulation. It is characterized by high hardness and slow dissolution of gelatin, along with its smooth surface for tablet formulation.

Polysaccharides, anionic and cationic surfactants, preservatives, and surface-active agents in formulation containing color, the surface of the static bed during the granulation process in the presence of gelatin owing to its hydrophilic nature are susceptible to microbial contamination. Properly prepared solutions should al-

#### 4. *Acacia*

Acacia, also named as gum arabic, is a natural gum obtained from the acacia trees. It is a complex, loose aggregate of sugars and hemicelluloses. It is commercially available in a powdered form, a granular form, or as a spray-dried product. As a tablet binder, it is used in an aqueous solution or added in dried form before moistening with water. Acacia forms very hard tablets that disintegrate slowly. Aqueous solutions are susceptible to bacterial and enzymatic degradation. It is incompatible with amidopyrine, cresol, phenol, ethanol, ferric salts, and with several other substances. Acacia, which was widely used in the past as a tablet binder, has been replaced by many synthetic polymers.

#### 5. *Tragacanth*

Tragacanth is a naturally occurring dried gum. It poses problems similar to those of acacia. Dry addition to the blend followed by addition of water works better than addition in solution, this is because of the difficulty in preparing the solution and the use of mucilage.

#### 6. *Alginic Acid*

Alginic acid is a polymannuronic acid extracted from seaweed. It is used as a binder and disintegrating agent at concentration between 1 and 5%. It slowly hydrolyzes at room temperature and is insoluble in water. Therefore, it is best incorporated in a dry state. It is incompatible with strong-oxidizing agents. It forms insoluble alginates with the alkaline earth metals and group III metals, with the exception of magnesium. These alginates may delay disintegration of the tablets owing to their gelling properties.

#### 7. *Sodium Alginate*

Sodium alginate slowly dissolves in water to form a viscous solution. A 3–5% solution is used in wet granulation process. It has also been used in sustained-release formulations because it delays the dissolution of a drug from tablets. It is hygroscopic, and its aqueous solution is susceptible to microbial contamination.

### B. *Synthetic Polymers*

#### 1. *Polyvinylpyrrolidone*

Polyvinylpyrrolidone (PVP, povidone) is a versatile and one of the most commonly used binders. It is readily soluble in water and freely soluble in

alcohol and many other organic solvents. It is available in variety of grades of different molecular weight. Povidone is generally used in the form of a solution; however, it can be added to the blends in the dry form and then granulated in situ. The in situ method generally requires a higher concentration of povidone to achieve the same binding effect of a solution. Povidone is frequently used as a binder in effervescent and chewable tablets because the tablets manufactured using PVP generally harden with age. Aqueous or hydroalcoholic solutions of povidone are used to granulate water-insoluble materials, and alcoholic solutions are used for granulating water-soluble materials. It is used as a binder at concentration between 0.5 and 5%. Low- to medium-viscosity grades are preferred for its use as a binder. It is highly hygroscopic and picks up significant amounts of moisture at low relative humidities.

## 2. Methylcellulose

Methylcellulose is a long-chain, substituted cellulose in which approximately 27–32% of the hydroxyl groups are in the form of methyl ether. It is available in a variety of grades of different degrees of substitution and average molecular weight. Therefore, it offers considerable latitude in binding strength. Efficiency of methylcellulose as a binder improves with the increasing molecular weight. Low or medium viscosity grades are preferred when used as a binder. It may be added as a dry powder or in solution. Although an aqueous solution of 1–5% can be used to granulate soluble or insoluble excipients, it is a better binder for soluble excipients, such as lactose and mannitol. Methylcellulose produces granulations that compress easily. Granulations produced using 5% methylcellulose solution are equivalent in hardness to 10% starch paste. It produces robust tablets, with a moderate hardness that does not increase with age.

Methylcellulose is practically insoluble in hot water, ethanol, chloroform, ether, and saturated salt solutions. In cold water, it swells and disperses slowly to form clear to opalescent, viscous dispersion. To produce aqueous solution, an appropriate quantity of methylcellulose powder is suspended in 25% of the required amount of water at 80°C. The remaining amount of water is added cold, or ice water is added to the hot slurry, with vigorous stirring to cool it to 20°C. A clear aqueous solution of methylcellulose is obtained. Methylcellulose can also be added as a dry powder to another powder before mixing with cold water. The methylcellulose can be moistened with an organic solvent, such as 95% ethanol before addition of water.

## 3. Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC) is a propyleneglycol ether of methylcellulose. It is available in variety of viscosity grades. Its binding prop-

erties are comparable with those of povidone. A 5% w/w may be used as a binder. It is soluble in cold water and forms a clear aqueous solution, HPMC is dispersed in water at 80–90°C with vigorous stirring to produce the required volume. Hydroalcoholic solutions of HPMC are other water-miscible solvent, such as ethanol. HPMC is first dispersed in water, then the required volume of solvent is added to produce the required volume of solution.

## 4. Sodium Carboxymethylcellulose

Sodium carboxymethylcellulose (Na-CMC) is a methyl ether of cellulose. It is available in a variety of grades which influence the viscosity. Na-CMC easily disperses in water at all temperatures. Its aqueous solubility varies with the average number of hydroxyl groups substituted. A 5–15% solution may be used to granulate their water solubility. The granulations are softer, but have good compressibility. Na-CMC is highly compressible. A quantity (> 50%) of water at 80°C is used using Na-CMC as a binder. It is incompatible with strongly acidic and alkaline materials, aluminum, zinc, and others.

## 5. Ethylcellulose

Ethylcellulose, an ethyl ether of cellulose, that differ in their viscosity. Ethylcellulose concentrations of 2–10% in water are used that compress into tablets the active ingredient from cellulose is insoluble in water. It is used in an ethanolic solution for water-sensitive formulations. Ethylcellulose, which were introduced in the 1980s, have been used for formulations requiring sustained-release pro-



s available in variety of grades generally used in the form of a ends in the dry form and then ally requires a higher concen- ding effect of a solution. Povi- rrescent and chewable tablets P generally harden with age. vidone are used to granulate itions are used for granulating r at concentration between 0.5 are preferred for its use as a significant amounts of moisture

1 cellulose in which approxi- in the form of methyl ether. It nt degrees of substitution and s considerable latitude in bind- as a binder improves with the 1 viscosity grades are preferred s a dry powder or in solution. be used to granulate soluble or or soluble excipients, such as ces granulations that compress yllcellulose solution are equiv- roduces robust tablets, with a th age.

in hot water, ethanol, chloro- ld water, it swells and disperses dispersion. To produce aqueous llulose powder is suspended in °C. The remaining amount of o the hot slurry, with vigorous solution of methylcellulose is d as a dry powder to another methylcellulose can be mois- thanol before addition of water.

propyleneglycol ether of meth- osity grades. Its binding prop-

erties are comparable with those of methylcellulose. Concentrations of 2–5% w/w may be used as a binder in either wet or dry granulation processes. It is soluble in cold water and forms a viscous colloidal solution. To prepare an aqueous solution, HPMC is first hydrated in 20–30% of required amount of water at 80–90°C with vigorous stirring. Cold water is added to produce the required volume. Hydroalcoholic solutions or mixtures of water and other water-miscible solvent, such as glycol, can also be used to dissolve HPMC. HPMC is first dispersed in the organic solvent, at a ratio of five to eight parts of solvent to one part of HPMC. Cold water is then added to produce the required volume. HPMC is incompatible with some oxidizing agents.

#### 4. Sodium Carboxymethylcellulose

Sodium carboxymethylcellulose (Na-CMC) is a sodium salt of carboxy- methyl ethers of cellulose. It is available in variety of molecular weights, which influence the viscosity of the solution and its swelling properties. It easily disperses in water at all temperatures to form a clear colloidal solution. Its aqueous solubility varies with its degree of substitution, which is the average number of hydroxyl groups substituted per anhydroglucose unit. A 5–15% solution may be used for the granulation of powders, regardless of their water solubility. The granulations produced using Na-CMC as a binder are softer, but have good compressibility. It forms tough tablets of moderate hardness. Na-CMC is highly hygroscopic material. It can adsorb a large quantity (> 50%) of water at high relative humidities. Therefore, the tablets using Na-CMC as a binder have tendency to harden with age. Na-CMC is incompatible with strongly acidic solutions and with metal salts of iron, aluminum, zinc, and others.

#### 5. Ethylcellulose

Ethylcellulose, an ethyl ether of cellulose, is available in variety of grades that differ in their viscosity. Low-viscosity grades are used as binders in concentrations of 2–10% in ethanol. Ethylcellulose produces softer granules that compress into tablets that easily disintegrate. However, the dissolution of the active ingredient from these tablets may be slower because ethylcel- lulose is insoluble in water. Ethylcellulose may be used in a dry form or as an ethanolic solution for wet granulation. It is a good nonaqueous binder for water-sensitive formulations. Aqueous polymeric dispersions of ethyl- cellulose, which were introduced for controlled-release coating application in the 1980s, have been used a binding agent for granulating products re- quiring sustained-release properties.

## 6. Polyethylene Glycol

Polyethylene glycols (PEGs), by themselves, have limited-binding action; however, they can enhance effectiveness of tablet binders and impart plasticity to granules. They can also be used in thermoplastic granulations. In this process, a powder blend containing 10–15% w/w of PEG-6000 is heated to 70°–75°C to obtain a paste-like mass that forms granules if stirred while cooling. This technique is used in lozenge formulations.

## 7. Polymethacrylates

Polymethacrylates (Eudragit NE 30D and Eudragit RS 30D) can be used as binders in aqueous or nonaqueous wet granulation processes. They are supplied as 30% aqueous dispersions. Dilution with water before use is recommended. Eudragit RS 30D is incompatible with magnesium stearate.

## 8. Polyvinyl Alcohol

Polyvinyl alcohols (PVAs) are available in variety of viscosity grades. Viscosity ranges from 10 to 100 cp lend themselves for tablet granulations. PVAs are water-soluble polymers. They form softer granulations which yield tablets that do not harden with age.

# C. Sugars

## 1. Glucose (Dextrose)

Glucose, when applied as syrup in concentrations above 50% in wet granulation processes, exhibits good-bonding properties. It produces moderately strong granules and tablets that are, however, hard and brittle. Glucose is also used as a direct compression tablet diluent and binder, primarily in chewable tablets. Anhydrous dextrose adsorbs substantial amounts of moisture at 25°C and 85% relative humidity to form a monohydrate. The monohydrate also absorbs moisture at 85% relative humidity. Dextrose is a reducing sugar and, in its aldehyde form, can react with amines, amides, amino acids, and such. Brown coloration may occur in the tablets containing dextrose and strong alkali or amines. This browning is called a Maillard reaction, which is a reaction between reducing sugars and proteins and is most common in candy preparation.

## 2. Sucrose

Sucrose is commercially available in several forms, such as granular, fine granular, fine, superfine, and confectioners sugar. The confectioners sugar

# Binders and Solvents

(contains 5% starch) is most commonly used in wet granulation processes. Sucrose syrup, containing 50–60% sucrose, is granulated with water or hydroalcoholic mixtures as granulation liquid. It produces strong, but brittle granules. The amount of liquid determines the tablet hardness. Sucrose is highly hygroscopic. Tablets containing sucrose may result in slow dissolution. If overwetting occurs, the amount of liquid must be carefully monitored. Sucrose may lead to incompatibility with the tablet quality. Sucrose is also unstable in the presence of acids. Contamination may lead to incompatibility with other ingredients.

## 3. Sorbitol

Sorbitol, a sugar alcohol, is highly hygroscopic at relative humidity above 60%. It is used as a humectant in pharmaceutical formulations. Sorbitol is also used as a moisture-control agent. Up to 2–20% of sorbitol can be used in wet granulation formulations.

# III. FACTORS INFLUENCING GRANULATION

The function of binders in a granulation process is to reduce friability of granules and to improve the effectiveness of a binder in a granulation process. The concentration, viscosity, mechanical strength, and other excipients in the formulation influence the binder and the substrate,

## A. Binder Concentration

During wet granulation process, the granule strength increases with increasing binder concentration in a formulation.

Figure 1 shows a plot of granule strength versus binder concentration. The granule strength increases with increasing binder concentration and reaches a maximum at a certain binder concentration. Beyond this concentration, the granule strength decreases.

...s, have limited-binding action; tablet binders and impart plasticity in thermoplastic granulations. In 5% w/w of PEG-6000 is heated and forms granules if stirred while in formulations.

...udragit RS 30D) can be used as binder in granulation processes. They are supplied with water before use is recommended with magnesium stearate.

...variety of viscosity grades. Viscosity values themselves for tablet granulations. A softer granulations which yield

...ations above 50% in wet granulation processes. It produces moderately hard and brittle. Glucose is a solvent and binder, primarily in tablets substantial amounts of moisture form a monohydrate. The monohydrate is hygroscopic. Dextrose is a reducing sugar. It reacts with amines, amides, amino acids in the tablets containing dextrose. Browning is called a Maillard reaction. Sugars and proteins and is most

...al forms, such as granular, fine crystalline sugar. The confectioners sugar

(contains 5% starch) is most commonly used in wet granulation formulations. Sucrose syrup, containing 50–67% w/w sucrose, is used as a binder in wet granulation processes. It can also be used as a dry binder in which it is granulated with water or hydroalcoholic solutions. Similar to glucose, sucrose produces strong, but hard and brittle, tablets. The amount of binder determines the tablet hardness. Softer granules can be obtained by using hydroalcoholic mixtures as granulating solutions. Finely divided sugar is hygroscopic. Tablets containing large amounts of sucrose may harden with age, which may result in slower disintegration. In the systems in which quick overwetting occurs, the amount and the rate of addition of the sucrose syrup must be carefully monitored. Use of sucrose with starch paste may improve the tablet quality. Sucrose is incompatible with aluminum. It hydrolyzes in the presence of acids. Contamination of powdered sucrose with heavy metals may lead to incompatibility with substances such as ascorbic acid.

### 3. Sorbitol

Sorbitol, a sugar alcohol, is the optical isomer of mannitol. It is highly hygroscopic at relative humidities of 65% and higher; therefore, it is used as a humectant in pharmaceutical formulations. Whenever this property of sorbitol as a moisture-control agent is desirable, it can be used as a binder. Up to 2–20% of sorbitol can be added as 10–25% aqueous solution in wet granulation formulations.

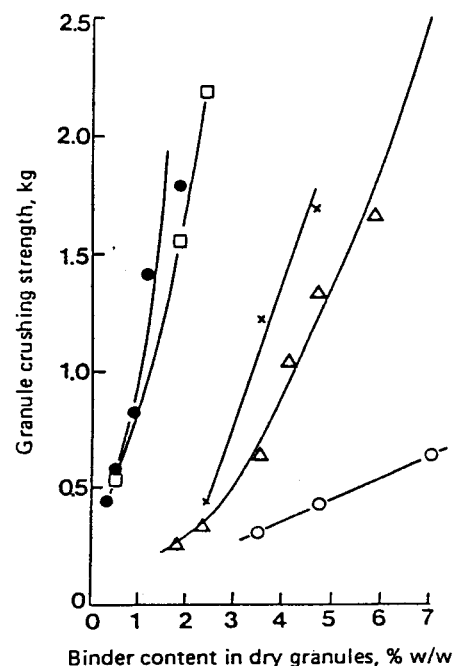
## III. FACTORS INFLUENCING BINDER EFFICIENCY

The function of binders in a tablet formulation is to impart strength and to reduce friability of granules and tablets. A multitude of factors influence the effectiveness of a binder in a formulation. Some of these factors are concentration, viscosity, mechanical properties of the binder, properties of a drug and other excipients in the formulation, interparticulate interactions between the binder and the substrate, and binder distribution.

### A. Binder Concentration

During wet granulation process, binder forms an internal matrix. Consequently, the granule strength and the tablet strength increases as the binder concentration in a formulation increases.

Figure 1 shows a plot of crushing strength of dicalcium phosphate granules versus binder concentration for various binding agents [5]. As the binder concentration increases, the crushing strength of the granules in-



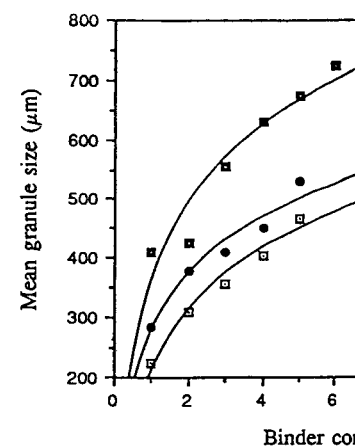
**Fig. 1** Crushing strength of wet granulated dicalcium phosphate. Binders: ●, gelatin; □, potato starch mucilage; x, acacia; Δ, povidone; ○, PEG 4000. (From Ref. 5.)

creases. The plot also shows that starch and gelatin can produce much stronger granules with lower concentrations, compared with acacia, PVP, or PEG 4000. As expected, the particle size of granules also increases as the binder concentration increases. Figure 2 shows a plot of mean particle size of lactose granules versus binder concentration [6].

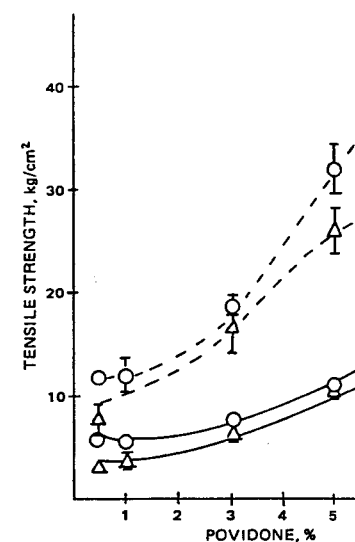
Intragranular bonds (formed during drying of granules) that are not fractured during compaction, cohesion of binder film and particles, and binder substrate adhesion are the types of bondings that contribute to the tablet strength. Jarosz and Parrott [7] showed that the radial and axial tensile strengths of the dicalcium phosphate tablets increased with increasing concentrations of povidone in the formulation (Fig. 3).

## B. Mechanical Properties of the Binder

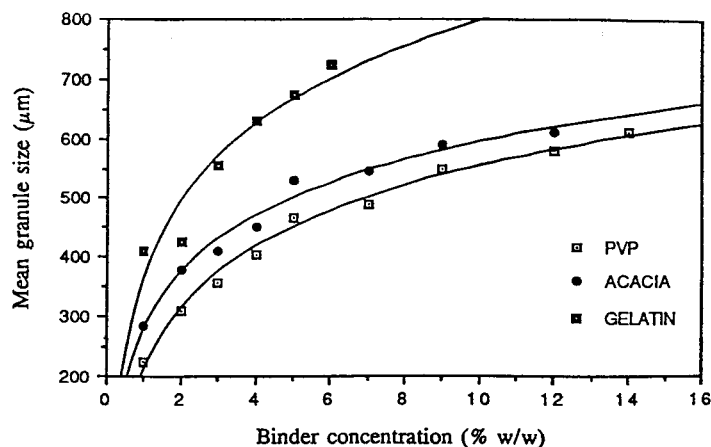
The mechanical and film-forming properties of a binder determines the strength and deformation behavior of a binder matrix. These properties of



**Fig. 2** Plot of the mean granule size of lactose. (From Ref. 6.)



**Fig. 3** The influence of povidone on the tensile strength of dicalcium phosphate dihydrate compacts. (From Ref. 7.)



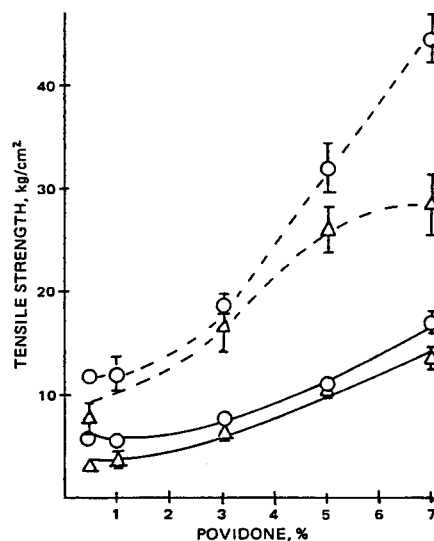
**Fig. 2** Plot of the mean granule size as a function of binder concentration for the granulation of lactose. (From Ref. 6.)

calcium phosphate. Binders: ●, gel-povidone; ○, PEG 4000. (From

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**Fig. 3** The influence of povidone on the tensile strength of tablets of dibasic calcium phosphate dihydrate compressed at 2268 (solid line) and at 4536 kg (dashed line); Δ, axial; ○, radial. (From Ref. 7.)



and the viscosity of the solution. During wet massing and the stages of drying, the drug and any soluble excipients will dissolve and then recrystallize, forming solid interparticulate bridges as the binder vehicle is evaporated. The strength of the crystalline bridges depends on the amount deposited and rate of crystallization. Both these properties are dependent on the solubility of the drug and other excipients in the granulating solvent. Consequently, the binder solvent will influence the granule formation and growth during wet massing, and the structure of the granules if the drug is soluble in the vehicle.

Wells and Walker [11] reported the effect of wet-massing acetylsalicylic acid with aqueous and hydroalcoholic solutions of PVP. The greater drug solubility produced granules of larger size, tighter particle size distribution, and reduced friability. The friability of the tablets was not reduced by secondary binding caused by solute deposition. High drug solubility in the binder solution produced tablets with poor disintegration properties.

#### D. Binder–Substrate Interactions

Major determinants of granule and tablet strength are wettability of the substrate by the binder, binder cohesion, and binder–substrate adhesion [10,12,13]. Rowe [14–16], in a series of publications, presented theoretical approaches to predict the binder–substrate interactions. Rowe showed that for a low-polarity substrate, such as griseofulvin, either PVP or starch would be the optimal binder, whereas for high-polarity substrates, such as theophylline, acacia or HPMC would be the optimal binder. This approach is based solely on the hypothesis that optimum spreading of the binder is the main criterion for successful formulation. It does not take into account other equally important factors, such as disintegration, dissolution, and flow properties. However, the study shows the potential of using the theoretical approach in binder selection and formulation optimization.

Parker et al. [17] studied the interactions during wet granulation between microcrystalline cellulose and aqueous solutions of two molecular weight grades of PVP and of HPMC. They showed that the rheological behavior of the granulations indicated that the behavior of the two molecular weight grades of the same polymer at equivalent viscosity was different. The differences were explained on the basis of differences in the surface tension, intragranule porosity, and polymer adsorption of HPMC on microcrystalline cellulose.

### E. Binder Distribution

The distribution of binder in the granules influences its ability to produce strong and nonfriable granules. The factors that resist the distribution of the

binder solution during wet granulation reduce the efficiency of the binder. For example, very viscous binder solutions, such as starch paste, may produce more friable granules and tablets.

The processing methods used to distribute the binder can influence the binder efficiency. Seager et al. [18,19] and Rue et al. [20] compared the granules and tablets of acetaminophen prepared by wet massing, dry granulation (i.e., roller compaction), and spray-drying of the substrate-binder slurry. Hydrolyzed gelatin was used as a binder. The distribution of the binder influenced the strength and rate of disintegration and dissolution of the tablets. Wet massing produced a sponge-like matrix that embedded substrate particles, whereas the roller compaction produced a distribution of discrete particles in the substrate particles. Spray-drying coated the granules with an outer shell of the binder. Spray-drying produced tablets that were superior to the other two methods.

During wet massing, the binder may be dissolved in the granulating solvent, which is then added to the powder blend. The binder can also be mixed dry with the powder blend, and the granulating solvent is added to the mixture. During the latter process, the binder is dissolved in the solvent in situ. This process may produce local points of high viscosity in the blend that may oppose distribution of the binder. This may lead to incomplete dissolution of the binder. Consequently, the dry blending of the binders, generally, requires higher concentration of the binder in the formula.

In a fluid bed granulation process, the factors influencing the droplet size of the binder solution must be carefully controlled because the granule size is directly related to the droplet size. Thus, the concentration and viscosity of the binder solution and the type of binder used will determine the particle size of the granules in a fluidized bed process.

The effectiveness of the binder is related to various factors related to the properties of the binder, properties of the drug substance, type of granulating solution, interaction between the binder and the substrate, and the processing method used. Consequently, it is difficult to predict the effect of a particular binder in a particular system. Thus, the effectiveness of a binder must be experimentally evaluated.

## REFERENCES

1. A Wade, PJ Walker, eds. *Handbook of Pharmaceutical Excipients*. 2nd ed. London: Pharmaceutical Press, 1994.
2. HA Lieberman, L Lachman, JB Schwartz, eds. *Pharmaceutical Dosage Forms: Tablets*. Vol 1, 2nd ed. New York: Marcel Dekker, 1989.
3. HG Kristensen. In: *Binders*; York: Marcel Dekker, 1993.
4. RW Mendes, SB Roy. *Tablets*.
5. NA Armstrong, GA March.
6. BD Rohera, A Zahir. Granules: their concentrations on the granule size and binder concentration.
7. PJ Jarosz, EL Parrott. *Factors affecting the strength of tablets*. J Pharm Sci 71:607, 1982.
8. JNC Healey, MH Rubinstein. *Binders used in tableting*. J Pharm Sci 71:607, 1982.
9. RF Shangraw, DA Demaree. *Formulation and manufacturing of tablets*. 1993.
10. I Krycer, DG Pope, JA Hershey. *Solution binders*. Powder Technology 1:1, 1981.
11. JI Wells, CV Walker. *The role of binders in tablet properties*. J Pharm Sci 71:607, 1982.
12. I Krycer, DG Pope, JA Hershey. *Pressure binders*. Powder Technology 1:1, 1981.
13. SJ Readind, MS Spring. *Tablet properties*. J Pharm Sci 71:607, 1982.
14. RC Rowe. *Binder-substrate interaction based on surface free energy*. J Pharm Sci 71:607, 1982.
15. RC Rowe. *Surface free energy model system*. Int J Pharm 1:1, 1981.
16. RC Rowe. *Polar/non-polar interaction with polymer binding agents*. J Pharm Sci 71:607, 1982.
17. MD Parker, P York, RC Rowe. *Tablet properties*. J Pharm Sci 71:607, 1982.
18. H Seager, I Burt, J Ryder, P Seager. *Technol Prod Manuf* 1:36, 1981.
19. H Seager, PJ Rue, I Burt, P Seager. *Manuf* 2:41, 1981.
20. PJ Rue, H Seager, J Ryder, P Seager. *Manuf* 2:41, 1981.



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3. HG Kristensen. In: Binders; Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker, 1993, pp. 451-465.
4. RW Mendes, SB Roy. Tableting excipients, Part II. Pharm Technol 3:61, 1978.
5. NA Armstrong, GA March. J Pharm Sci 65:200, 1976
6. BD Rohera, A Zahir. Granualtions in a fluidized-bed: effect of binders and their concentrations on the granule growth and modeling relationship between granule size and binder concentration. Drug Dev Ind Pharm 19:773, 1993.
7. PJ Jarosz, EL Parrott. Factors influencing axial and radial strength of tablets. J Pharm Sci 71:607, 1982.
8. JNC Healey, MH Rubinstein, V Walter. The mechanical properties of some binders used in tableting. J Pharm Pharmacol Suppl 26:41P, 1974.
9. RF Shangraw, DA Demarest Jr. A survey of current industrial practices in the formulation and manufacture of tablets and capsules. Pharm Technol 17:32, 1993.
10. I Krycer, DG Pope, JA Hersey. An evaluation of tablet binding agents. Part I. Solution binders. Powder Technol 34:39, 1983.
11. JI Wells, CV Walker. The influence of granulating fluids upon granule and tablet properties: the role of secondary binding. Int J Pharm 15:97, 1983.
12. I Krycer, DG Pope, JA Hersey. An evaluation of tablet binding agents. Part II. Pressure binders. Powder Technol 34:53, 1983.
13. SJ Readind, MS Spring. The effects of binder film characteristics on granule and tablet properties. J Pharm Pharmacol 36:421, 1984.
14. RC Rowe. Binder-substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. Int J Pharm 52:149, 1989.
15. RC Rowe. Surface free energy and polarity effects in the granulation of a model system. Int J Pharm 53:75, 1989.
16. RC Rowe. Polar/non-polar interactions in the granulation of organic substrates with polymer binding agents. Int J Pharm 56:117, 1989.
17. MD Parker, P York, RC Rowe. Binder-substrate interactions in wet granulation. 2: The effect of binder molecular weight. Int J Pharm 72:243, 1991.
18. H Seager, I Burt, J Ryder, PJ Rue, S Murray, N Beal, JK Warrack. Int J Pharm Technol Prod Manuf 1:36, 1979.
19. H Seager, PJ Rue, I Burt, J Ryder, JK Warrack. Int J Pharm Technol Prod Manuf 2:41, 1981.
20. PJ Rue, H Seager, J Ryder, I Burt. Int J Pharm Technol Prod Manuf 1:2, 1980.

Pharmaceutical Excipients. 2nd ed.

eds. Pharmaceutical Dosage Forms: Dekker, 1989.

# 5

## Spray Drying as an Alternative Granulation Technique

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## I. INTRODUCTION

Among the numerous granulation techniques, spray drying stands out as unique. It is the only process that directly converts a liquid into a dry powder in a single step. This method removes moisture instantly and converts pumpable liquid into dry powder. In addition to the relative simplicity of this method, there are several inherent advantages to the process making it ideal for handling a wide variety of products.

### A. Background

This process has been employed for decades and found its earliest widespread acceptance in the dairy industry. Spray dryers to produce powdered milk, whey, and baby formulas are still one of the largest applications of the technology. The advantages listed in the following, however, have provided incentive for producers of a wide variety of products to develop the process for their specific needs.

### B. Advantages

Spray drying is a continuous process. As long as liquid feed can continue to be supplied to the drying system the powder product will continue to be produced. In some instances, this process has been operated for months without interruption.

The actual spray-drying process is very rapid, with the major portion of the evaporation taking place in less than a few seconds. This minimal exposure time combined with evaporative cooling, creates a very lenient process relative to thermal effects. As a result, spray drying is well suited for heat-sensitive products.

Probably the greatest advantage of spray drying arises in that selection of equipment choices and manipulation of process variables gives the operator a degree of control over the physical properties of the powder produced.

Lastly spray dryers have few moving parts. In fact, careful selection of various components can result in a system having no moving parts in direct contact with the product.

## II. SPRAY DRYER IN PHARMACEUTICALS

Spray drying has been used in the pharmaceutical industry since the 1940s for producing drug substances and various excipients. Spray drying, being a

## Spray Drying as a Granulation

continuous process, did not fit the result, it was employed primarily for fine chemicals, such as antibiotics in the pharmaceutical industry, however, to reduce manufacturing cost, and the highest level of quality. Spray drying reduces the labor-intensive formulation of dose pharmaceuticals gives case in numerous instances.

Evaluation of spray-drying has been reported by various authors. It has been used to produce microencapsulated substances, food ingredients, and the technique to produce enteric-coated vinyl alcohol microparticles for oral onyl human growth hormone and thymotropin-releasing hormone microparticles of biodegradable polymers in publications.

Until recently, the spray drying has been used for production of pharmaceuticals because of the continuous nature of the process. The shut-down of the process because of maintenance with any continuous process, is not produced to justify the investment.

A second factor that no longer hinders the development of computer-based monitoring and recording of the process simultaneously. This has brought the continuous process to a level for automation.

The spray-drying process is ideal for product handling and operation. Potent compounds are considered that eliminate the workers contact with the product. Products with high volume requirements for pharmaceuticals are good candidates for spray drying. The technique has been used for the granulations of magnesium carbonate [28], and sulfaethylthiazole in a polymer matrix [30,31]. Spray drying

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continuous process, did not fit well in the "series of batches" concept. As a result, it was employed primarily in manufacture of bulk pharmaceuticals and fine chemicals, such as antibiotics, analgesics, antacids, and vitamins. The pharmaceutical industry, however, is coming under ever-increasing pressure to reduce manufacturing cost, while still maintaining strict purity standards and the highest level of quality control. The fact that spray drying greatly reduces the labor-intensive formulation, drying, and granulating of solid-dose pharmaceuticals gives cause to review the potential for this process in numerous instances.

Evaluation of spray-dried lactose over conventionally prepared lactose has been reported by various authors [1,2]. Spray drying as a process has been used to produce microencapsulated and matrix formulations of drug substances, food ingredients, and flavoring [3-19]. Use of the spray-drying technique to produce enteric-coated pentapeptide of thymopentin [20], polyvinyl alcohol microparticles for aerosol application [21], recombinant methionyl human growth hormone and tissue-type plasminogen activator [22], and thymotropin-releasing hormone containing injectable sustained-release microparticles of biodegradable polymers [23] have been reported in recent publications.

Until recently, the spray-drying process, was considered inappropriate for production of pharmaceutical dosage forms. The main concerns being the continuous nature of the process; the amount required for start-up and shut-down of the process because of the cost of the drug substance; and as with any continuous process, the volume of product that may have to be produced to justify the investment and the space and installation requirement.

A second factor that now makes spray drying more attractive is the development of computer-based control systems. This allows continuous monitoring and recording of a very large number of process variables simultaneously. This has brought the degree of quality control of this continuous process to a level formerly obtainable only by batch operators.

The spray-drying process, owing to its automated setup, offers minimal product handling and operator exposure to dust. As more and more potent compounds are considered for commercial production, processes that eliminate the workers contact with the drugs become more desirable. Products with high volume requirements, such as over-the-counter pharmaceuticals are good candidates for the spray-drying process. Spray-drying technique has been used for granulating [24,25]; for slow-release granulations of magnesium carbonate [26], theophylline [27], acetaminophen [28], and sulfaethylthiazole [29]; and for spray congealing with a wax matrix [30,31]. Spray drying has been used for changing the biopharma-

ceutical properties, such as the dissolution rate of a poorly soluble drug [32–35].

### III. SPRAY-DRYING PRINCIPLES

There are three fundamental steps involved in spray drying. The first is atomization of a liquid feed into fine droplets. Second, mixing of these spray droplets with a heated gas stream, allowing the liquid to evaporate and leave dried solids. The solidified particles usually have the same size and shape as the atomized droplet. Binders, such as wax or polymers, dispersants, and soluble salts, may help hold these spheres together. Finally, the dried powder is separated from the gas stream and collected. The spent drying gas is treated to meet environmental requirements and then exhausted to the atmosphere or, in some cases, recirculated back to the system (i.e., closed-cycle plant).

#### A. Atomization

Atomization is the process by which a liquid is disintegrated into many fine droplets, thereby yielding a very high surface/mass ratio. This is an ideal situation for drying because evaporation is most readily accomplished from a surface film of liquid. Ideally, the droplets would all be of the same size. This goal has not yet been attained, but it has been closely approached in the laboratory. On a commercial basis the distribution of droplet sizes is sufficiently narrow to achieve the goals of the drying process.

##### 1. Mechanism

Over the years several researchers have studied the mechanism by which atomization takes place and several theories have evolved. The most widely accepted explanations are based on the liquid jet theory described in 1878 by Lord Rayleigh [36], whose work was for the breakup of nonviscous liquid in a laminar flow region. The simplest way to view this mechanism in everyday life is to watch the droplet formation from a dripping faucet. A liquid stream accelerated by the force of gravity is pulled apart or disintegrated into droplets which at first are connected by thin strings, but eventually break apart into teardrop-shaped droplets. The surface tension of the liquid causes the droplet, suspended in air, to form itself into a sphere. Should a thin string connecting two droplets break away from both, it will be formed into a much smaller droplet. Considerable work has followed to incorporate the effects of viscosity and turbulence as experienced in commercial applications [42].

#### 2. Commercial Atomization

Just as the dripping faucet atomizes water, commercial systems employ other methods. Common of these are kinetic energy, sonic energy, and vibrations. Sonic energy and vibrations have found a few commercial applications.

Kinetic energy is applied in pneumatic atomization. This is probably the most common within the pharmaceutical industry due to the interaction of the liquid with the gas. Neither the liquid nor the air is heated, being typical. Figure 1 is a typical pneumatic atomizer varying the ratio of the compressed air to the liquid. The main advantage of this form of atomization is low velocity as it exits the nozzle, allowing a long flight path for drying. Because of the relatively small systems, pneumatic atomization is the simple design that lends itself to minimal contamination. Pneumatic atomization must be given to supply the stringent requirements for sterility. Typical particle distributions are depicted in Fig. 2.

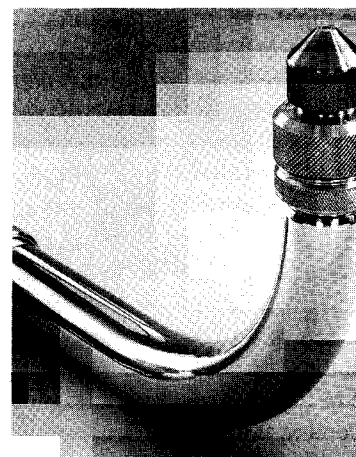


Fig. 1 A typical two-fluid nozzle.

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## 2. Commercial Atomization Techniques

Just as the dripping faucet atomizes a liquid by the force of gravity, commercial systems employ other forces to create an atomized spray. The most common of these are kinetic energy, pressure energy, and centrifugal energy. Sonic energy and vibrations have also been studied, but as yet have found few commercial applications.

Kinetic energy is applied in the form of two-fluid or pneumatic atomization. This is probably the most commonly used atomization technique within the pharmaceutical industry. Here, atomization is accomplished by the interaction of the liquid with a second fluid, usually compressed air. Neither the liquid nor the air require very high pressure, with 200–350 kPa being typical. Figure 1 is a two-fluid nozzle. Particles size is controlled by varying the ratio of the compressed airflow to that of the liquid [41]. The main advantage of this form of atomization is that the liquid has a relatively low velocity as it exits the nozzle; therefore, the droplets require a shorter flight path for drying. Because many pharmaceutical applications use relatively small systems, pneumatic nozzles are often used. Another advantage is the simple design that lends itself to easy cleaning, sterile operation, and minimal contamination. Pneumatic nozzles can be designed to meet the most stringent requirements for sterile or aseptic applications. Special consideration must be given to supply a sterile source of compressed air for atomization. Typical particle distribution range for various atomization techniques are depicted in Fig. 2.

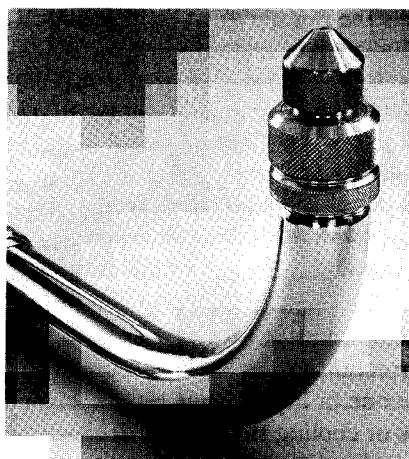
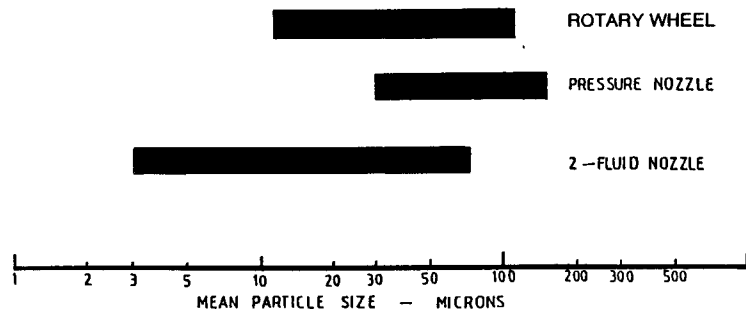


Fig. 1 A typical two-fluid nozzle used for atomization.



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**Fig. 2** Range of mean particle sizes achievable by control of atomizer operation at low to medium feed rates.

The second most common form of atomization for pharmaceutical applications is hydraulic pressure nozzle atomization, a pressure nozzle with diagrams of the internal ports is shown in Fig. 3a and b. Here the liquid is pressurized by a pump and forced through an orifice to break the liquid into fine droplets. The differential pressure across the orifice determines the mean droplet diameter [40]. The distribution about the mean is similar, but in most instances is more narrow than with two-fluid atomization. As the liquid spray exits the nozzle with a relatively high velocity, a spray-drying chamber of at least 2.5 m in diameter and 3.0 m in cylinder height is usually required to operate with pressure nozzles. Antibiotics are a typical application for such a dryer.

Centrifugal atomization uses a rotating disk or wheel to break the liquid stream into droplets. Figure 4 depicts the flight path of a single droplet exiting the wheel. These devices normally operate in the range of 5,000–25,000 rpm with wheel diameters of 5–50 cm. The size of the droplets produced is nearly inversely proportional to the peripheral speed of the wheel. The distribution of particle sizes about the mean is fairly constant for a given method of atomization, but the mean itself can be varied from as small as 15  $\mu\text{m}$  to as large as 250  $\mu\text{m}$ , depending on the amount of energy transmitted to the liquid. The mass flow of the liquid, its viscosity, solids content, and surface tension influence particle size directly, but none to the degree of peripheral wheel velocity. Consequently, an increase in feed rate may slightly increase the particle size, but use of a variable-speed drive on the centrifugal atomizer facilitates correction to the specified size.

Centrifugal atomizers, similar to the one in Fig. 5, have been designed to minimize contamination from lubricants or cooling fluids [37]. Because the feed material is in direct contact with rotating parts, the application of this technology is limited. There also must be a rather large production require-

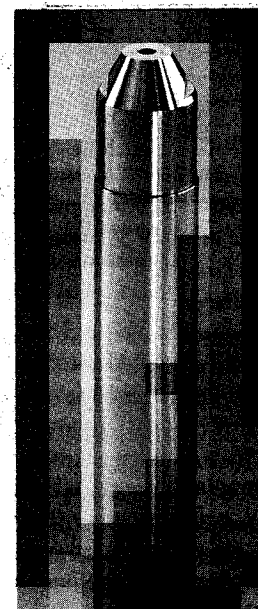
## Spray Drying as a Granulation

ment if coarse powders are of fine chemicals, such as antacids,

The resulting spray-dried [38], each with identical compo in a porous shell of soluble mate and, unless intentionally produce relatively low density and friab compaction. Reproducibility fro to the next, is excellent.

## B. Mixing and Drying

Once the liquid is atomized it the heated gas for evaporation t droplets. This contact step tak chamber. The heated gas is intro which ensures that the gas flow



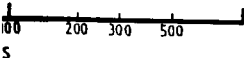
(a)

**Fig. 3** (a) Typical pressure nozzle of a typical pressure nozzle. (Cour

 ROTARY WHEEL

 PRESSURE NOZZLE

 2-FLUID NOZZLE



ble by control of atomizer operation

tomization for pharmaceutical ap-  
mization, a pressure nozzle with  
Fig. 3a and b. Here the liquid is  
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ss the orifice determines the mean  
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Consequently, an increase in feed  
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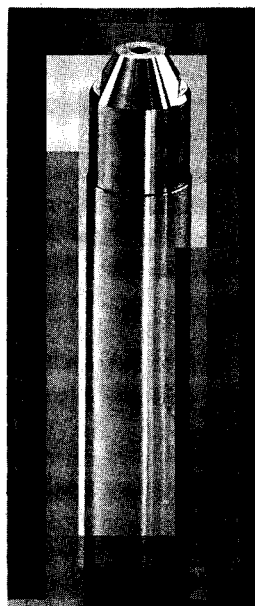
one in Fig. 5, have been designed  
or cooling fluids [37]. Because the  
ting parts, the application of this  
a rather large production require-

ment if coarse powders are of interest. Bulk pharmaceutical excipients and fine chemicals, such as antacids, are often produced by this technique.

The resulting spray-dried powder consists of many spherical particles [38], each with identical composition and having suspended solids encased in a porous shell of soluble material. The particles are generally free-flowing and, unless intentionally produced with very fine atomization, dust-free. The relatively low density and friability of the particles makes them ideal for compaction. Reproducibility from batch to batch, and even from one dryer to the next, is excellent.

## B. Mixing and Drying

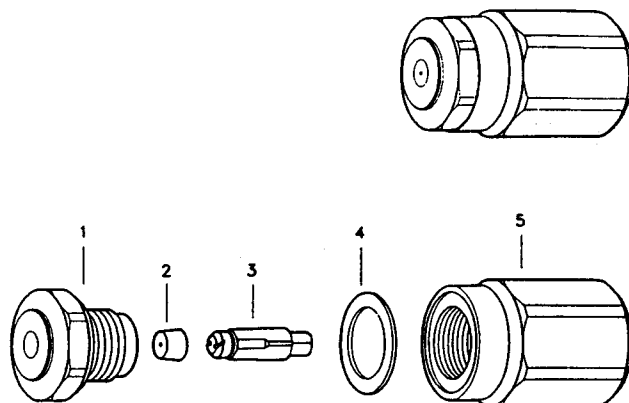
Once the liquid is atomized it must be brought into intimate contact with the heated gas for evaporation to take place equally from the surface of all droplets. This contact step takes place within a vessel called the drying chamber. The heated gas is introduced into the chamber by an air disperser, which ensures that the gas flows equally to all parts of the chamber.



(a)

**Fig. 3** (a) Typical pressure nozzle used for atomization; (b) internal components of a typical pressure nozzle. (Courtesy of Spraying Systems Co., Wheaton, IL.)





ITEM	PART NO.	DESCRIPTION
1	CP37729-SS	CAP, STAINLESS STEEL
2	SIA*	ORIFICE INSERT, SPECIALLY TREATED HARDENED STAINLESS STEEL
	SIY*	ORIFICE INSERT, Y CARBIDE
3	SKA*	CORE WITH SPECIALLY TREATED HARDENED STAINLESS STEEL CORE TIP
	SKY*	CORE WITH Y CARBIDE CORE TIP
4	CP1268-FV	GASKET, FIBER (STANDARD)
	CP1268-AL	GASKET, ALUMINUM (OPTIONAL)
	CP1268-NY	GASKET, NYLON (OPTIONAL)
5	CP37667-SS	NOZZLE BODY, STAINLESS STEEL (FOR 1/4SK)
	CP37668-SS	NOZZLE BODY, STAINLESS STEEL (FOR 3/8SK)
No. 1/4SK**, SPRAYDRY® NOZZLE		
No. 3/8SK**, SPRAYDRY® NOZZLE		

\* SPECIFY ORIFICE INSERT OR CORE No.

\*\* SPECIFY ORIFICE INSERT AND CORE Nos.

(b)

Fig. 3 Continued

### 1. Air Disperser

The air disperser uses perforated plates or vaned channels through which the gas is directed, creating a pressure drop and, thereby, equalizing the flow in all directions. It is critical that the gas entering the air disperser is well mixed and has no temperature gradient across the duct leading into it. Should such a gradient be present, drying will be uneven within the chamber, resulting in wet deposits, damaged product, or both. As a result, it is important that any type of heater used inherently produces a well-mixed gas stream, or that a mixing section is placed between the heater and the air disperser.

### Spray Drying as a Granulation

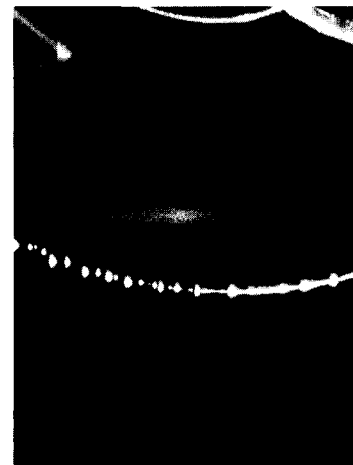
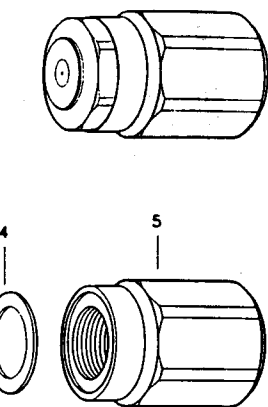


Fig. 4 A liquid stream from a nozzle breaking up into droplets.

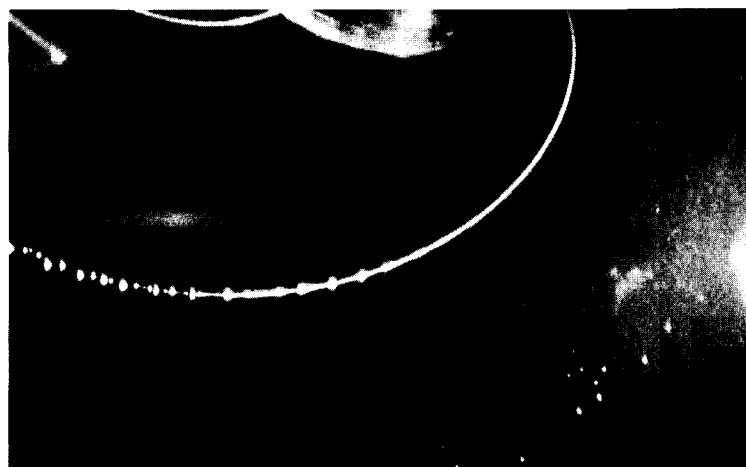
The air disperser is normally placed at the outlet of the atomization device is placed at the inlet. This arrangement allows instant mixing of the solid with the atomized cloud of droplets.

To fully understand the mechanism of spray drying, one needs to examine the mechanism of droplet formation. Physically, there are many very small droplets. When the droplet is first exposed to the hot air, the material dissolved in the liquid begins to evaporate from the surface of the sphere. Although the droplet is cool, as the liquid concentration decreases, the rate of evaporation increases. Evaporation then takes place over the entire surface of the sphere. This process is called spray drying or is said to be diffusion-controlled. The droplet is in the cooler part of the dryer, where the temperature of the dryer is lower than the inlet temperature. As the droplet moves toward the outlet, it becomes heated above the outlet temperature. The temperature may be considerably higher. The droplet is approximately 20°C lower than the inlet temperature of the dryer, which is necessary for the droplet to be exposed to elevated temperatures. The selection or modification of additives is recommended on each formulation.



DESCRIPTION
TREATED HARDENED STAINLESS STEEL
TREATED HARDENED STAINLESS STEEL CORE TIP
TIP
(L)
HEEL (FOR 1/4SK)
HEEL (FOR 3/BSK)

or vaned channels through which  
up and, thereby, equalizing the flow  
entering the air disperser is well  
ross the duct leading into it. Should  
e uneven within the chamber, re-  
or both. As a result, it is important  
roduces a well-mixed gas stream,  
n the heater and the air disperser.

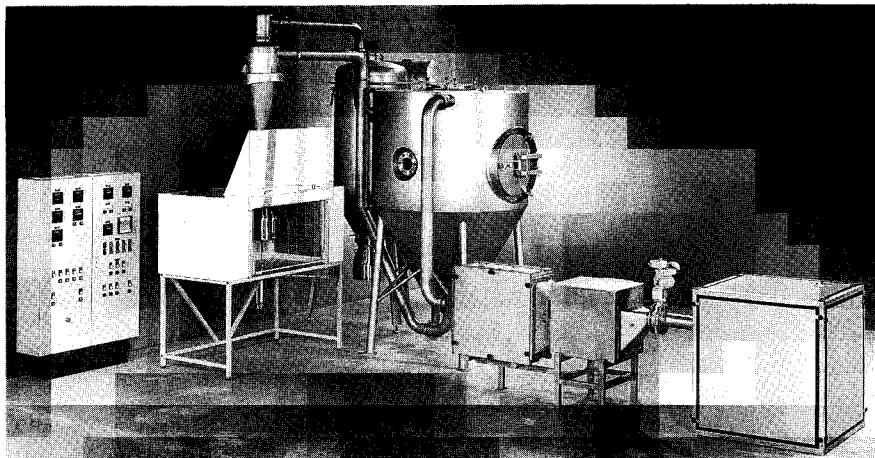


**Fig. 4** A liquid stream from a centrifugal atomizer wheel as it breaks up into fine droplets.

The air disperser is normally built into the roof of the drying chamber and the atomization device is placed in or adjacent to the air disperser. This arrangement allows instant and complete mixing of the heated drying gas with the atomized cloud of droplets.

To fully understand the characteristics of spray-dried powders, one needs to examine the mechanism for drying within a single droplet. Typically, there are many very small particles suspended in a sphere of liquid. When the droplet is first exposed to hot gas, rapid evaporation takes place. Material dissolved in the liquid will tend to form a thin shell at the surface of the sphere. Although the evaporation has kept the particle itself quite cool, as the liquid concentration decreases, the particle will begin to heat. Evaporation then takes place only as quickly as the liquid can diffuse to the surface of the sphere. This phase of the drying process is called *first-order* drying or is said to be diffusion-rate-limited. Fortunately, this phase occurs in the cooler part of the dryer where the drying gas is at or near the outlet temperature of the dryer. As a result the solids in each particle are never heated above the outlet temperature of the dryer, even though the dryer inlet may be considerably higher. The final dried powder will be at a temperature approximately 20°C lower than the air outlet temperature. Turbulence within the dryer, which is necessary for good drying, does cause some particles to be exposed to elevated temperatures. This sometimes causes a loss in activity or modification of additives such as binders. Therefore, test work is recommended on each formulation, and the best combination of inlet and outlet





**Fig. 6** A typical spray dryer setup showing the chamber, the cyclone and exhaust gas filters, and product collection vessel. (Courtesy of Niro A/S, Denmark and Niro Inc., Columbia, MD.)

The second criteria is that all droplets must be sufficiently dried before they contact a surface. This is where the vessel shape comes into play. Centrifugal atomizers require larger diameters and less cylinder height. Nozzles are just the opposite. Most spray dryer manufacturers can estimate, for a given powder's mean particle size, what dimensions are needed to prevent wet deposits on the drying chamber walls. Meeting both criteria often results in an oversized dryer. Such a chamber has greater volume than that required by the production rate, but is minimally sized to contain the atomized spray pattern, thereby maintaining clean chamber walls.

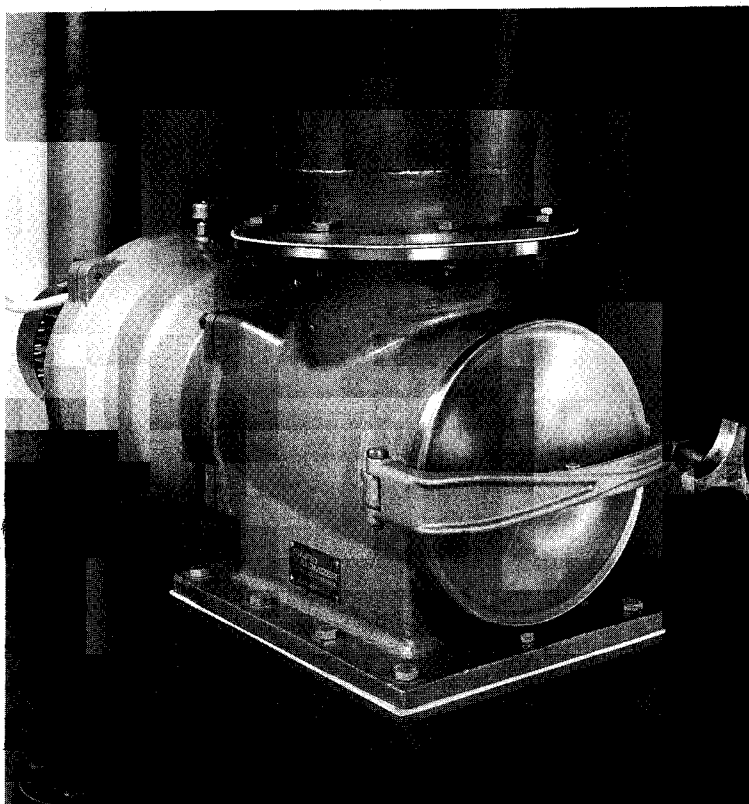
Drying chambers are usually constructed of stainless steel sheet metal, with stiffeners for structural support and vessel integrity. Sheet steel finish and weld polish can be specified to meet any requirement. Insulation is usually applied to the outside of the vessel, and a stainless steel sheet wrapping is seam-welded over the entire vessel. This provides a thermally efficient and safe system that is easy to clean and has no crevice areas that might become contaminated.

### C. Powder Separation

In almost every case, spray-drying chambers have cone bottoms to facilitate the collection of the dried powder. When coarse powders are to be collected, they are usually discharged directly from the bottom of the cone [39] through

a suitable airlock, such as a rotary valve (Fig. 7). The gas stream, now cool and containing all of the evaporated moisture, is drawn from the center of the cone above the cone bottom and discharged through a side outlet. In effect, the chamber bottom is acting as a cyclone separator. Because of the relatively low efficiency of collection, some fines are always carried with the gas stream. These must be separated in high-efficiency cyclones, followed by a wet scrubber or in a fabric filter (bag collector). Fines collected in the dry state (bag collector) are often added to the larger powder stream or recycled.

When very fine powders are being produced, the side outlet is often eliminated and the dried product together with the exhaust gas are transported from the chamber through a goose neck at the bottom of the cone. The higher loading of entrained powder may affect cyclone design, but has little or no effect on the bag collector size.



**Fig. 7** Rotary valve air lock used at the discharge port of the drying chamber. (Courtesy of Niro A/S, Denmark and Niro Inc., Columbia, MD.)

## E. The Complete System

For pharmaceutical applications, the use of gases is usually not considered. In drying these products, combinations of heat sources may have an overall production cost for the heat source. Steam heating coils, stainless steel, finned tube heat exchangers may be required. Electric heating elements may be required. Electric heating elements may be required.

Figure 6 depicts a typical spray drying system. The system is kept under slight negative pressure to prevent escaping any possible leaks. The system is kept under slight negative pressure to prevent escaping any possible leaks. The system is kept under slight negative pressure to prevent escaping any possible leaks.

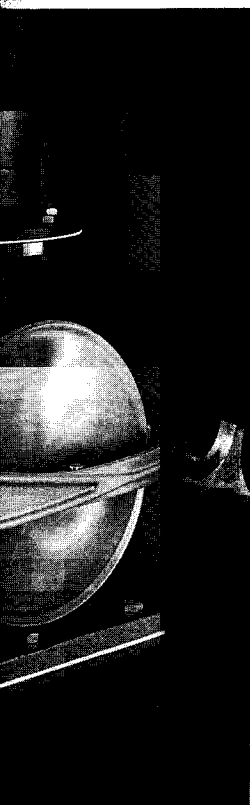
In a pharmaceutical drying system, the use of gases is usually not considered. Coarse filters are used to filter incoming air or the air used before exhausting air from the system with even a small amount of dust.

There are an almost infinite number of spray dryers. These can be used as control loops, or part of a larger system. They operate a complete manufacturing process. They offer great advantage in the monitoring of many process variables. A control system in a process screen of an automatic system, is shown in Fig. 9.

## IV. SOME SPECIAL SYSTEMS

The possible particle size range of the mean particle diameters from the mean is generally described

Fig. 7). The gas stream, now cool, is drawn from the center of the chamber and through a side outlet. In effect, the gas stream is drawn through a separator. Because of the relatively low temperatures carried with the gas stream, the gas stream is always carried with the gas stream. cyclones, followed by a wet scrubber. The gas stream is collected in the dry state (bag filter) or recycled. The gas stream, produced, the side outlet is often used with the exhaust gas are transferred through the neck at the bottom of the cone. The gas stream may affect cyclone design, but has



charge port of the drying chamber.  
(Columbia, MD.)

## E. The Complete System

For pharmaceutical applications, direct contact of product with combustion gases is usually not considered. The relatively low temperatures used for drying these products, combined with the small influence that energy costs have on overall production costs, makes steam or electricity common choices for the heat source. Steam heating is normally accomplished by means of stainless steel, finned tube heat exchangers. Filters before and after the heater may be required. Electric heaters require filters and may have to have sheathed heating elements to prevent contamination.

Figure 6 depicts a typical pharmaceutical system. Drying gas is moved through the system by conventional industrial fans. A combination of push and pull fans is often used to effect a near neutral pressure in the drying chamber. Dampers and controls are used to balance the system. Consideration must be given to the desired direction for possible leaks. Normally, a system is kept under slight negative pressure to prevent dust from potentially escaping any possible leaks. This would certainly seem to be true for handling potent compounds. On the other hand, sterile systems often cannot tolerate in-leaks of room air, because only the final discharge point is located in the clean room.

In a pharmaceutical dryer, filtration of the drying gas is an important consideration. Coarse filters are almost always used to remove airborne dust, dirt, and such. High-efficiency particulate air (HEPA) filters may be required to filter incoming air or the air after heating. HEPA filters are also sometimes used before exhausting air from the system if there are hazards associated with even a small amount of powder escaping to the atmosphere.

There are an almost infinite variety of control systems available for spray dryers. These can be as simple as a small panel with two or three control loops, or part of a large distributed control system (DCS), which operates a complete manufacturing facility. These computer-controlled systems offer great advantage in quality control and validation. Continuous monitoring of many process variables is possible, and trend analysis is often employed. A control system interface panel is shown in Fig. 8, and a typical process screen of an automated control system, depicting all the process variables, is shown in Fig. 9.

## IV. SOME SPECIAL SYSTEMS

The possible particle size range of spray-dried powders is represented by mean particle diameters from 20 to about 200  $\mu\text{m}$ . The distribution about the mean is generally described by having approximately 80% of the parti-



Fig. 8 Control panel for a typical spray dryer. (Courtesy of Niro A/S, Denmark.)

cles between 0.5 and 2.0 times the mean diameter. This varies somewhat, depending on atomization technique and formulation. Powders with a mean particle diameter larger than  $75\text{ }\mu\text{m}$  can usually be said to be free-flowing and nondusty. Such powders can be easily fed to conventional tableting equipment, producing equivalent, or in some cases better, quality tablets than other granulation methods [25]. Most pharmaceutical granulation is still done batch-wise and usually results in larger particles than spray dryers produce.

One of the most popular of these techniques is fluid bed spray granulation, which is described in detail in Section VI. There is now a process that combines features of both spray drying and fluid bed granulation to achieve a continuous process that produces granules similar to those obtained from a fluid bed granulation process. This process is called fluidized spray drying (FSD). An FSD system is shown in Fig. 10. In principle, the operation is much like a conventional spray dryer. However, the bottom cone of the spray dryer has been modified to include an integral fluid bed. In the upper part of the fluidized spray dryer, atomization and mixing with heated air takes place as usual. However, when the partially dried particles fall from the drying gas, they are captured in a fluidized bed. Controlled temperature and humidity conditions in the bed allow the particles to stay moist enough to agglomerate. Each of these agglomerates are a cluster of individual partially spray-dried droplets.

## Spray Drying as a Granulation

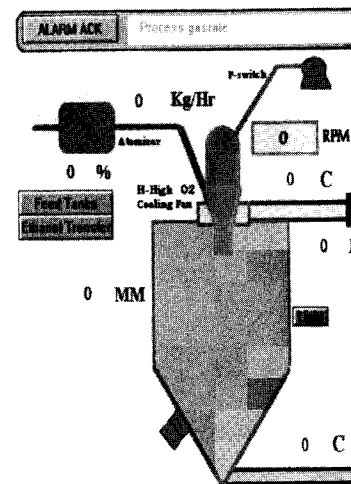


Fig. 9 A control system screen. (Courtesy of Niro Inc., Columbus, Ohio.)

Obviously, there are granules without agglomerating. In addition, there is some attrition. Fines from the drying gas exhaust point, the air inlet and the fluidized bed are ducts in the roof. As a result, fines through the atomized spray, granulation. Fines that do escape are or a bag collector and pneumatic there are frequently no fines be internal to the system.

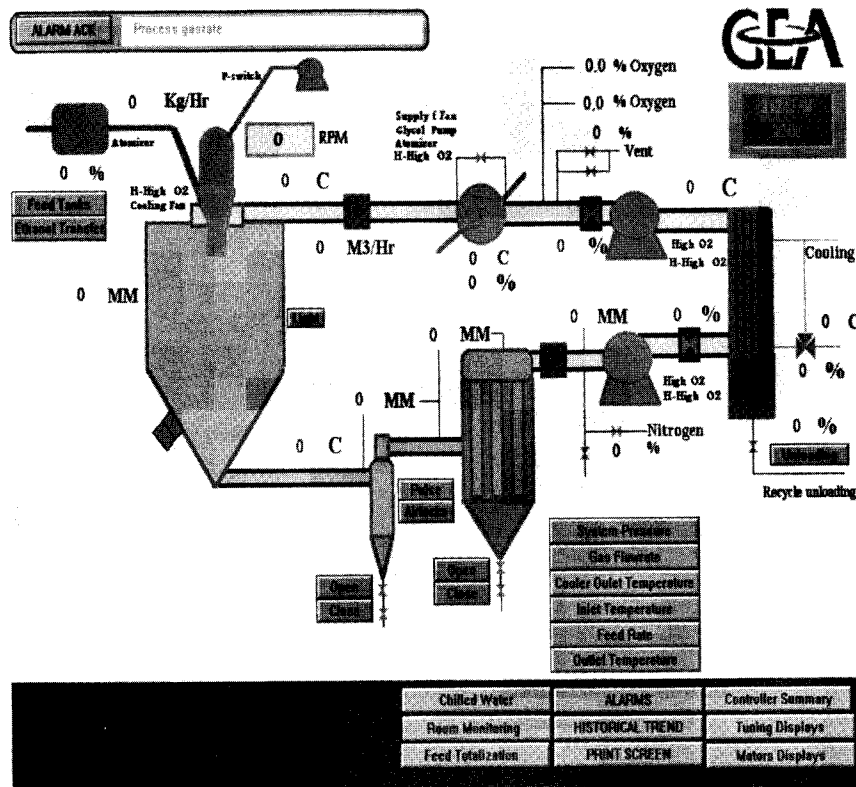
Compared with a conventional process, the integral fluid bed



(Courtesy of Niro A/S, Denmark.)

diameter. This varies somewhat, formulation. Powders with a mean usually be said to be free-flowing and to conventional tableting equipments better, quality tablets than other granulation is still done batch-wise than spray dryers produce.

Techniques is fluid bed spray granulation VI. There is now a process combining fluid bed granulation to produce granules similar to those obtained by fluid bed granulation. This process is called fluidized bed spray drying. In principle, the process is similar to fluid bed spray drying. However, the bottom cone of the fluid bed is replaced by an integral fluid bed. In the fluid bed, the particles are fluidized and mixing with heated air. The partially dried particles fall from the fluid bed. Controlled temperature is maintained to keep particles to stay moist enough. The particles are a cluster of individual par-

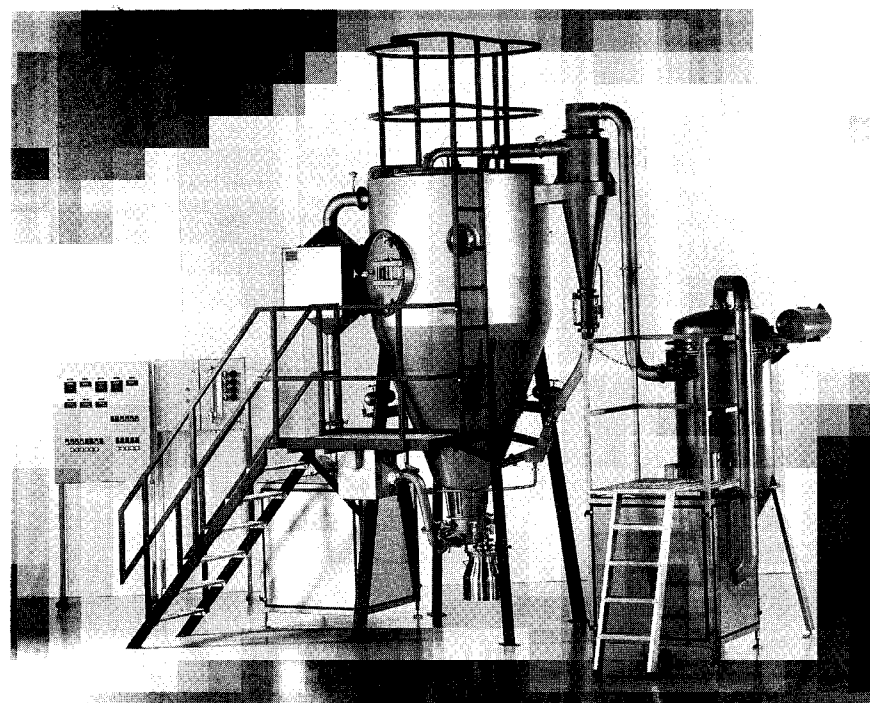


**Fig. 9** A control system screen showing a closed cycle spray-drying process. (Courtesy of Niro Inc., Columbia, MD.)

Obviously, there are going to be some droplets that dry completely without agglomerating. In addition, the fluidizing action in the fluid bed will create some attrition. Fines from both sources will tend to be carried toward the drying gas exhaust point. In the FSD, all drying gas from both the hot air inlet and the fluidized bed leave the drying chamber through two exhaust ducts in the roof. As a result, fines entrained in the gas stream have to pass through the atomized spray, affording even greater opportunity for agglomeration. Fines that do escape the drying chamber are collected in cyclones or a bag collector and pneumatically reinjected into the dryer. As a result there are frequently no fines left to recycle or discard. All fines recycled can be internal to the system.

Compared with a conventional spray dryer the FSD has more components. The integral fluid bed with its own air supply and the fines return





**Fig. 10** A fluidized spray dryer (FSD) system. (Courtesy of Niro A/S, Demark and Niro Inc., Columbia, MD.)

system add a number of items. Additional drying of the product may be necessary, if the moisture specification cannot be reached by the existing setup. Figure 11 represents the differences in spray-dried powder versus FSD. The product produced using FSD has a broader particle size distribution and a lower bulk density than the powders produced by other spray dryers.

It is not suggested that the FSD is a replacement for all spray-drying applications, but it does provide an alternative that expands the range and form of materials that can be produced. Typical FSD powders have mean agglomerate size from 150 to 400  $\mu\text{m}$ .

## V. SPRAY-DRYING SOLVENTS

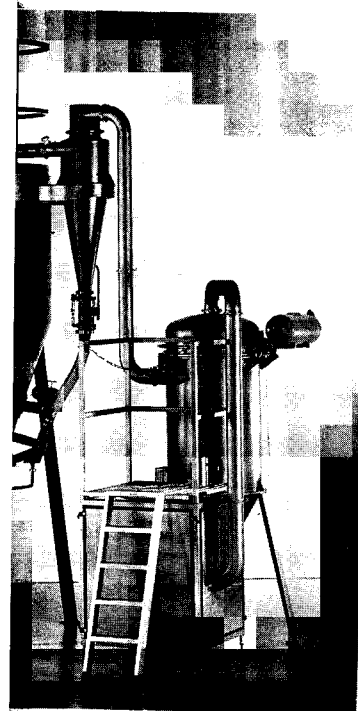
Up to this point, the terms *drying gas* and *air* have been used almost interchangeably. Also the product being dried is assumed to be suspended or



**Fig. 11** Comparison of product from spray dryer (FSD). (Courtesy of Niro Inc., Columbia, MD.)

dissolved in water. In pharmaceuticals, it is often desired to spray-dry hazardous solvents. Evaporating solvents in a hazardous environment is often hazardous. Consequently, there are many complications. For small drying units, the solvent can be collected without recirculation, and the solvent can be collected. For large units, this is expensive. As a result, a closed-cycle system is given. A closed-cycle system is given.

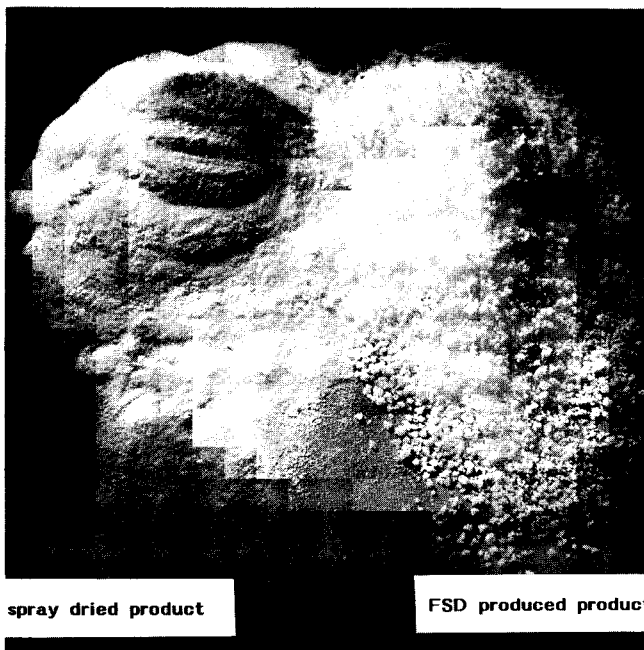
Closed-cycle systems have a drying chamber, and product and solvent are dried. In addition, they have a solvent recovery system. All of the evaporated solvent is collected. Such a system is practical only if the solvent is stable at the drying temperature and the drying



1. (Courtesy of Niro A/S, Demark

drying of the product may be not be reached by the existing spray-dried powder versus FSD. der particle size distribution and ced by other spray dryers. eplacement for all spray-drying ive that expands the range and pical FSD powders have mean

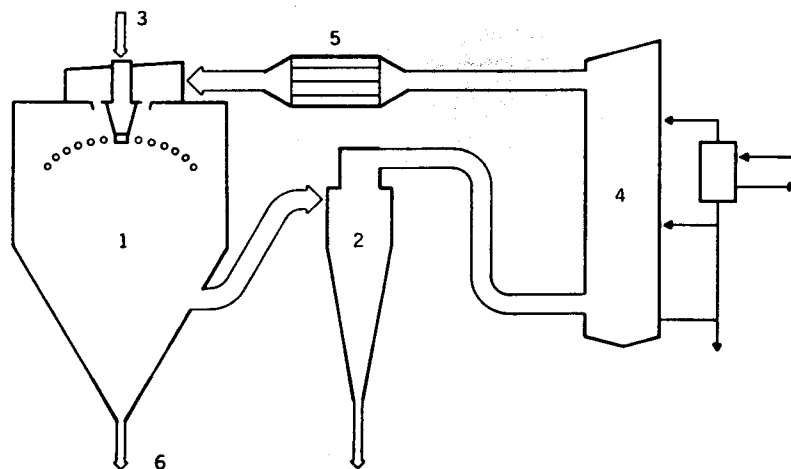
ir have been used almost inter- s assumed to be suspended or



**Fig. 11** Comparison of product produced by regular spray dryer and with fluidized spray dryer (FSD). (Courtesy of Niro Inc., Columbia, MD.)

dissolved in water. In pharmaceuticals, however, as in several other industries, it is often desired to spray dry a feedstock containing organic solvent. Evaporating solvents in a heated airstream, although very efficient, is very hazardous. Consequently, inert gas, usually nitrogen, is used for these applications. For small drying tests and laboratory work, the nitrogen can be used without recirculation, employing a carbon bed on the exhaust gas to collect the solvent. For larger applications, this would be prohibitively expensive. As a result, a closed cycle system is used. A simple flowsheet for a closed-cycle system is given in Fig. 12.

Closed-cycle systems have an indirect heater, gas disperser, drying chamber, and product and fines collection system similar to any other spray dryer. In addition, they have a condenser on the exhaust gas, which recovers all of the evaporated solvent. The nitrogen, which now contains only a small amount of solvent vapor, can be reheated and passed back through the dryer. Such a system is practical only if the difference between the condenser outlet temperature and the drying temperatures is sufficiently large to permit a



**Fig. 12** A typical layout of the closed-cycle spray dryer system: 1, drying chamber; 2, fines recovery; 3, feed; 4, scrubber/condenser; 5, drying gas indirect heater; 6, dried powder.

reasonable amount of evaporation for the recirculated nitrogen flow and still produce the required low residual volatile content in the spray-dried powder.

A wide variety of solvents have been used in spray drying applications. Occasionally, the solvent is selected based on its drying characteristics. For instance, the lower the boiling point of the solvent the lower the dryer outlet temperature can be. If a material is thermoplastic or particularly heat-sensitive, a low-boiling solvent may be the only choice. Often, however, the synthesis process upstream from the drying step determines the solvents. For instance in pharmaceuticals, alcohols, such as methanol, ethanol, and isopropanol, are used. In other industries ketones, such as acetone, methyl ethyl ketone, or methylisobutyl ketone, are used. Chlorinated solvents, particularly methylene chloride, were once popular, but are less used now owing to health and environmental concerns.

## VI. SPRAY DRYER GRANULATION

When compared with other granulation methods, spray drying stands out as unique in several ways. Because the feed to a spray dryer is a homogeneous liquid, it eliminates the concern over blending of dry components with liquids. An excess of liquid is always used, and all components can be well dispersed.

Additionally, this provides a spray-dried granule. Suspended in the same ratio in each part of granulation by particle size in a tablet components within a tablet will be uniform.

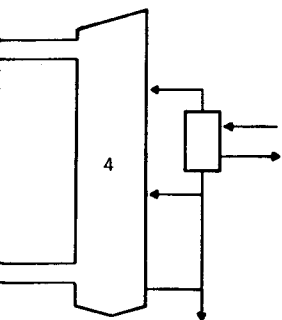
Many granulation methods require energy to convert very fine particles into granules. There are several drawbacks. First, different batch characteristics, even if particle size is uniform. This is true even if the equipment is spray drying, some trial and error combinations and liquid pressures are required when changing the scale of operation whether from a large dryer or a small properties such as bulk density.

Second, and most important, is the contact with moving parts. A large amount of energy is required in the proper cleaning of parts, lubrication, and parts replacement in the cleaning process. Lastly, although nozzle or centrifugal atomizers are used, they will not destroy microorganisms in shear granulators.

## VII. DEVELOPMENT

Before any spray-drying work is done, the ability of the application. This is done with a few simple tests. First, the material is measured, and a small sample is taken. It can be readily formed. If the material is indicating high viscosity, then it is not drying without formulation or by dilution or chemical-mechanical means.

Once drops can be formed, they are using a heated air gun. Air is used to serve for any stickiness, color, or passing this test, some powder is taken to determine the sticking point. If successful, the sticking point must be a dryer.



ray dryer system: 1, drying chamber;  
user; 5, drying gas indirect heater;

circulated nitrogen flow and still  
content in the spray-dried powder.  
used in spray drying applications.  
on its drying characteristics. For  
solvent the lower the dryer outlet  
ermoplastic or particularly heat-  
only choice. Often, however, the  
step determines the solvents. For  
as methanol, ethanol, and iso-  
es, such as acetone, methyl ethyl  
Chlorinated solvents, particularly  
ut are less used now owing to

hods, spray drying stands out as  
a spray dryer is a homogeneous  
ing of dry components with liq-  
and all components can be well

Additionally, this provides the highest degree of homogeneity in each spray-dried granule. Suspended and dissolved materials will all be present in the same ratio in each particle. As a result, even if there is some segregation by particle size in a tableting operation, the distribution of components within a tablet will be uniform.

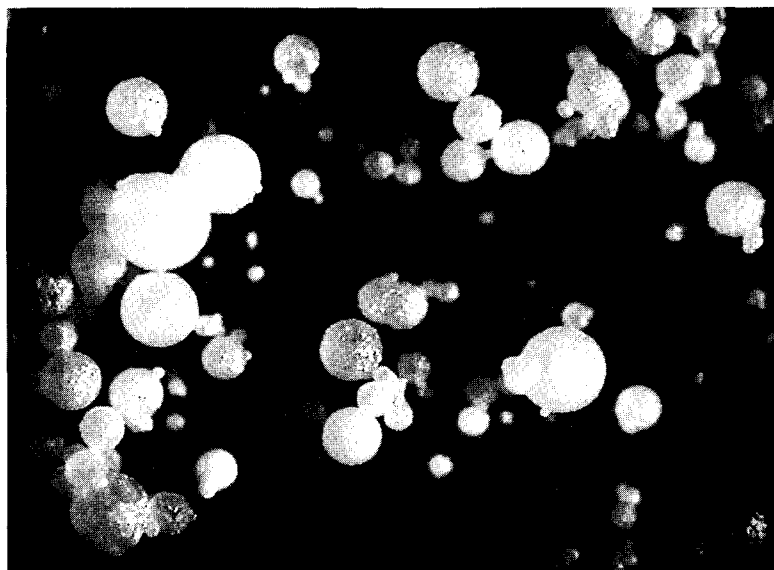
Many granulation methods depend on the application of mechanical energy to convert very fine powders into granules. This has three potential drawbacks. First, different batch sizes will yield different granule characteristics, even if particle size is maintained, particularly for compressibility. This is true even if the equipment is scaled exactly to the batch quantity. In spray drying, some trial and error is encountered in establishing nozzle combinations and liquid pressures to obtain equivalent particle size distribution when changing the scale of operation. The resulting powder, however, whether from a large dryer or a smaller dryer, will have very similar physical properties such as bulk density and compressibility.

Second, and most important, in a spray dryer, the product is never in contact with moving parts. Although just as much attention to detail is required in the proper cleaning of spray-drying systems, the absence of moving parts, lubrication, and parts with close tolerances, greatly facilitates the cleaning process. Lastly, although it is the application of shear forces in the nozzle or centrifugal atomizer that creates a spray, this form of energy generally will not destroy microencapsulated material as can happen in high-shear granulators.

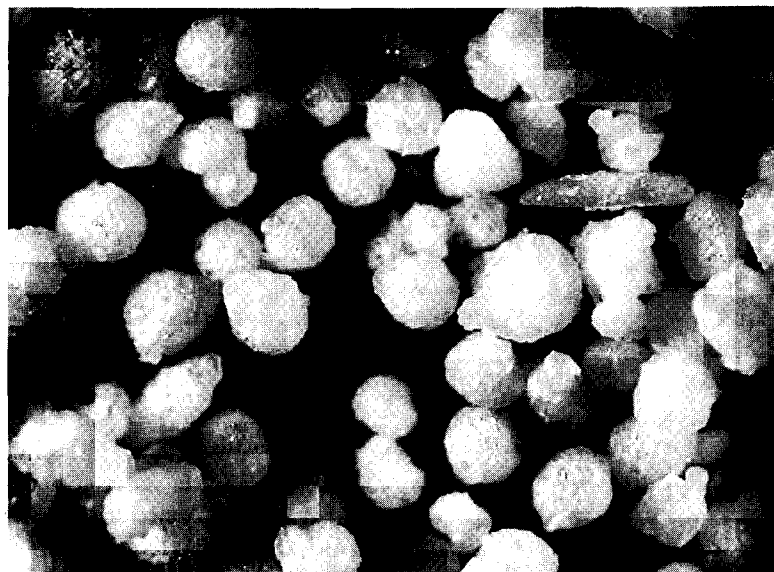
## VII. DEVELOPMENT

Before any spray-drying work begins, it is necessary to determine the feasibility of the application. This is often accomplished at the laboratory bench with a few simple tests. First, the viscosity of the solution or suspension is measured, and a small sample is tested to see if droplets from a stirring rod can be readily formed. If the liquid strings from the surface or forms peaks, indicating high viscosity, then the product may not be a candidate for spray drying without formulation changes. Viscosity reduction may be required, by dilution or chemical-mechanical methods.

Once drops can be formed, some product is dried on a glass slide using a heated air gun. Air temperature is recorded and the material is observed for any stickiness, color changes, or other changes as it dries. After passing this test, some powder is placed on a variable temperature hot bench to determine the sticking point of the powder. For spray drying to be successful, the sticking point must be higher than the outlet temperature of the dryer.

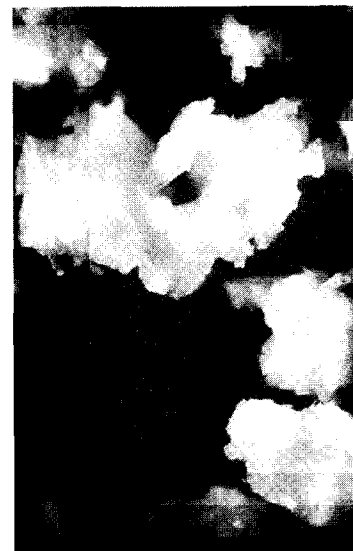


(a)



(b)

Fig. 13

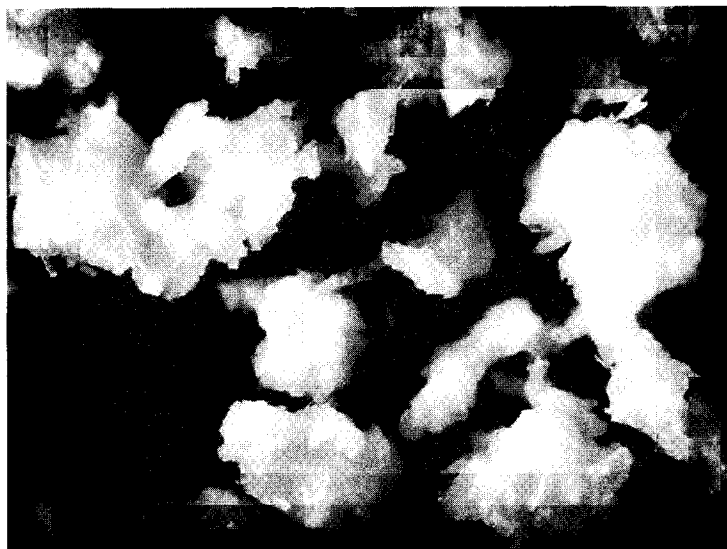
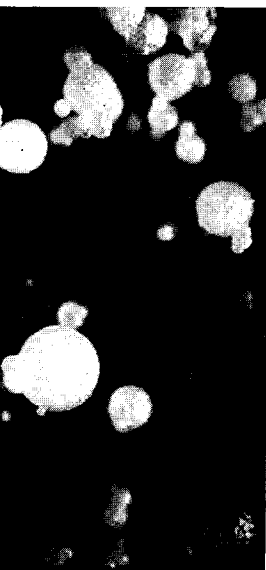


(c)

**Fig. 13** Spray-dried product (a) produced from a centrifugal atomization; (c) produced using fluid bed drying (Columbia, MD.)

If all seems well to this, a laboratory dryer of at least 100 ml. capacity should be used for tests. Bench-scale spray dryers provide a good opportunity for testing, however, combined with very good results, produce good samples for further testing, at for chemical stability to be tested in contact with heated air. A series of temperature combinations will be established. Although the effect of spray drying on laboratory dryer are not suitable for drying chamber dimensions, or

Production of coarser particles as a result, larger samples will be produced, product quality are usually do



(c)

**Fig. 13** Spray-dried product (a common anti-inflammatory drug with excipients): (a) produced from a centrifugal atomizer; (b) produced using pressure nozzle atomization; (c) produced using fluidized spray dryer (FSD). (Courtesy of Niro Inc., Columbia, MD.)

If all seems well to this point, a spray-drying trial is probably in order. A laboratory dryer of at least 500 mm in diameter should be used for such tests. Bench-scale spray dryers are available, but limited in their ability to provide a good opportunity for spray drying to succeed. The laboratory unit, however, combined with very fine atomization (two-fluid or rotary) will produce good samples for further testing. These samples should be looked at for chemical stability to be sure no damage has occurred as a result of contact with heated air. A series of tests performed at different inlet-outlet temperature combinations will determine the optimum conditions for further tests. A relation of outlet temperature versus final product moisture should be established. Although these samples tell the development team much about the effect of spray drying on the product, samples produced in a laboratory dryer are not suitable for direct compression; because of the small drying chamber dimensions, only fine powders can be produced.

Production of coarser powders will require a larger, pilot-scale dryer; as a result, larger samples will be needed. This is why initial screenings for product quality are usually done in the laboratory unit. Pilot-scale work also

has to be done in a spray-drying development center. Although many companies have laboratory dryers, few have the sizes and variety of process types needed to fully develop a production scheme. These facilities are usually found at spray-drying manufacturers or custom-processing companies. Besides having the equipment, manufacturers and custom processors also have the expertise to more quickly optimize the desired product characteristics. Powders produced in such a facility are shown in Fig. 13a-c.

## VIII. CONCLUSION

Spray drying can be an advantageous route to pharmaceutical manufacture. In the production of powders for direct compression tableting, this process continuously produces a product of uniform composition and controllable physical properties. It can often replace several steps from a traditional batchwise process and eliminate a considerable amount of operator handling.

It does require a certain degree of laboratory and pilot-scale testing. Unlike other granulation unit operations for which a single piece of equipment can be used for multiple products, the spray dryer plant must be custom designed and engineered to suit the product requirements and the upstream and downstream handling of the product. Unless considerable in-house expertise has been developed, the design and operation of a production plant will almost certainly require consultation through universities, manufacturers, or custom processors.

## REFERENCES

1. RA Castello, AM Mattocks. *J Pharm Sci* 51:106-108, 1962.
2. WC Gunsell, L Lachman. *J Pharm Sci* 52:178-182, 1963.
3. C Vollemy, P Speiser, M Soliva. *J Pharm Sci* 66:631-634, 1977.
4. PB Deasy. *Microencapsulation and Related Drug Process*. New York: Marcel Dekker, 1984, pp. 181-193.
5. F Neilson. *Manuf Chem July*: 38-41, 1982.
6. LA Luzzi, MA Zoglio, HV Maulding. *J Pharm Sci* 59:338-341, 1970.
7. R Bodmeier, H Chen. *J Pharm Pharmacol* 40:754-757, 1989.
8. DL Wise, GJ McCormick, GP Willet. *Life Sci* 19:867-874, 1976.
9. H Takenaka, Y Kawashima, SY Lin. *J Pharm Sci* 69:1388-1392, 1980.
10. H Takenaka, Y Kawashima, SY Lin. *J Pharm Sci* 70:1256-1260, 1981.
11. Y Kawashima, SY Lin, H Takenaka. *Drug Dev Ind Pharm* 9:1445-1463, 1983.
12. J Traue, H Kala. *Pharmazie* 39:233-237, 1984.
13. Y Kawashima, K Matsuda, H Takenaka. *J Pharm Pharmacol* 24:506-512, 1972.

## Spray Drying as a Granulation

14. M Rosenberg, IJ Kopelman. 1990.
15. M Rosenberg, IJ Kopelman.
16. H Takenaka, Y Kawashima. 2189-2195, 1982.
17. T Eldem, P Speiser, AA Hiri.
18. T Eldem, P Speiser, H Alto.
19. H Hauser, G Strauss. *Bioch*
20. R Gidwani, K Venkat, T . 385-394, 1992.
21. T Ting, I Gonda, EM Gipp.
22. M Mumenthaler, CC Hsu, I
23. S Takada, Y Uda, H Togch. 184, 1995.
24. JM Newton. *Manuf Chem*
25. AM Raff, MJ Robinson, E'
26. Y Kawashima, K Matsuda,
27. H Takeuchi, T Handa, Y J 1989.
28. M Becirevic, R Senjkovic,
29. AF Asker, CH Becker. *J P*
30. PM John, CH Becker. *J P*
31. IS Hamid, CH Becker. *J P*
32. H Takeuchi, T Handa, Y K
33. H Takeuchi, T Handa, Y K
34. OI Corrigan, EM Holohar. 1985.
35. H Junginger, M Wedler. A
36. K Masters. *Spray Drying* p. 172.
37. O Hansen. Aseptic non-c. presented at Nordisk R3 Sym
38. TL Lloyd. Atomization of University, UK, 1972.
39. JH Perry, CH Chilton, SD Section 20, New York, 19
40. *Spraying Systems Compa*
41. Delavan Manufacturing C ogy Brochure 678A-1269
42. WR Marshall. *Ind Eng C*

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1:106-108, 1962.

78-182, 1963.

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l Drug Process. New York: Marcel

2.

arm Sci 59:338-341, 1970.

40:754-757, 1989.

Sci 19:867-874, 1976.

rm Sci 69:1388-1392, 1980.

rm Sci 70:1256-1260, 1981.

Dev Ind Pharm 9:1445-1463, 1983.

1984.

J Pharm Pharmacol 24:506-512,

14. M Rosenberg, IJ Kopelman, Y Talmon. *J Agric Food Chem* 38:1288-1294, 1990.
15. M Rosenberg, IJ Kopelman, Y Talmon. *Food Sci* 50:139-144, 1985.
16. H Takenaka, Y Kawashima, Y Chikamatsu, Y Ando. *Chem Pharm Bull* 30: 2189-2195, 1982.
17. T Eldem, P Speiser, AA Hincal. *Pharm Res* 8:47-54, 1991.
18. T Eldem, P Speiser, H Altorfer. *Pharm Res* 8:178-184, 1991.
19. H Hauser, G Strauss. *Biochim Biophys Acta* 897:331-334, 1987.
20. R Gidwani, K Venkat, T Audhya, G Goldstein. *Drug Dev Ind Pharm* 18: 385-394, 1992.
21. T Ting, I Gonda, EM Gipps. *Pharm Res* 9:1330-1335, 1992.
22. M Mumenthaler, CC Hsu, R Pearlman. *Pharm Res* 11:12-20, 1994.
23. S Takada, Y Uda, H Togchi, Y Ogawa. *PDA J Pharm Sci Technol* 49:180-184, 1995.
24. JM Newton. *Manuf Chem Aerosol News* April: 33-36; 55, Volume 37, 1966.
25. AM Raff, MJ Robinson, EV Svedres. *J Pharm Sci* 50:76-79, 1961.
26. Y Kawashima, K Matsuda, H Takenaka. *J Pharm Sci* 63:1546-1551, 1974.
27. H Takeuchi, T Handa, Y Kawashima. *Drug Dev Ind Pharm* 15:1999-2016, 1989.
28. M Becirevic, R Senjkovic, I Usmani. *Pharmazie* 44:776-777, 1989.
29. AF Asker, CH Becker. *J Pharm Sci* 55:90-94, 1966.
30. PM John, CH Becker. *J Pharm Sci* 57:584-589, 1968.
31. IS Hamid, CH Becker. *J Pharm Sci* 59:511-514, 1970.
32. H Takeuchi, T Handa, Y Kawashima. *J Pharm Pharmacol* 39:769-773, 1987.
33. H Takeuchi, T Handa, Y Kawashima. *Chem Pharm Bull* 35:3800-3806, 1987.
34. OI Corrigan, EM Holohan, MR Reilly. *Drug Dev Ind Pharm* 11:677-695, 1985.
35. H Junginger, M Wedler. *Acta Pharm Technol* 30:68-71, 1984.
36. K Masters. *Spray Drying Hand Book*. New York: John Wiley & Sons, 1985, p. 172.
37. O Hansen. Aseptic non-contaminating spray drying of pharmaceuticals. Presented at Nordisk R3 Symposium, Elsignor, Denmark, March 24, 1971.
38. TL Lloyd. Atomization of liquid by rotary atomizers, PhD dissertation, Leeds University, UK, 1972.
39. JH Perry, CH Chilton, SD Kirkpatrick. *Chemical Engineers Handbook*. 4th ed. Section 20, New York, 1963.
40. Spraying Systems Company, Wheaton, IL.
41. Delavan Manufacturing Co., West Des Moines, Iowa. *Spray Droplet Technology Brochure* 678A-1269.
42. WR Marshall. *Ind Eng Chem* 45(1):47, 1953.



# 6

## Roller Compaction Technology

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## I. INTRODUCTION

The intent of this chapter, is to provide a thorough synopsis of compactor-operating principles, processing properties, and equipment design advantages that are presently used in manufacturing pharmaceutical solid-dosage forms. The chapter identifies and illustrates relevant compaction theory and practice pertaining to vacuum deaeration design technology and processing variables. Another objective is to create new ideas that can be translated into process and quality improvements to reduce product costs. It also aims to stimulate and influence researchers and vendors to advance the technology.

There may be some associated problems and challenges pertaining to the technology. Many of the problematic issues are addressed in this chapter. This is accomplished by explaining in detail, through the use of illustrative articles, and providing considerations and appropriate steps for technology personnel to take to achieve an optimized compaction process.

The practice of compacting is used in numerous industry segments: chemical, food, petrochemical, agriculture, pharmaceutical, steel, and non-

ferrous metals. Particulate emissions from these industries' economic impact is reduced in several ways:

- Eliminates dust
- Minimizes product loss
- Improves product quality
- Enhances reactions
- Improves storage and handling
- Preserves chemical stability

Formulation technology is undergoing revolutionary change. What process technology methods can be used to reduce cycle time, minimize the handling of materials, improve environmental operating-manageability, and reduce actions are focused to reduce the cost of goods.

The pharmaceutical industry is seeking a better understanding of the manufacturing process. Ideally, pharmaceutical manufacturing processes are acutely scrutinized to eliminate waste. Industry improvement demands that technologists be more effective in increasing productivity by targeting wasteful practices.

Worldwide pharmacopeias are being updated. Manufacturers' specifications are increasing. Granulations processed using traditional methods have specific physical properties to function correctly and quickly. Production rates for high-speed production are minute and for encapsulators, production rates are slow and economic concerns are vast.

Companies worldwide are seeking ways to improve their business to uncover ways to improve the quality of their products and services. For example, Halodan Antibiotic Ltd. (HAL) is using roller compaction instead of granulating technology. HAL's per capita production is increasing. The aim is to reduce antibiotic manufacturing costs, improve individual and overall productivity, and reduce the cost of day-to-day operations and

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appropriate steps for technology  
compaction process.  
in numerous industry segments:  
pharmaceutical, steel, and non-

ferrous metals. Particulate enlargement by compaction has a direct bearing on these industries' economies and performance of solids-handling systems in several ways:

- Eliminates dust
- Minimizes product loss
- Improves product movement
- Enhances reactions of gases, liquids, and solids
- Improves storage and handling
- Preserves chemical mixture uniformity

Formulation technology for pharmaceutical tablets and capsules is undergoing revolutionary changes. All companies are actively investigating what process technology methods can be used to shorten the manufacturing cycle time, minimize the handling and logistical activities, and reduce costly environmental operating-manufacturing space. All these ideas, concepts, and actions are focused to reduce manufacturing costs in the effort to lower the cost of goods.

The pharmaceutical industry is greatly emphasizing cost reduction and a better understanding of the solid materials' physical properties. Continually, pharmaceutical manufacturers' operating budgets and cost centers are acutely scrutinized to eliminate process wastes and excessive time delays. Industry improvement demands are driving equipment designers and process technologists to be more effective, more efficient, and to help boost productivity by targeting wasteful procedures and cutting costs.

Worldwide pharmacopeial tablet and capsule standards and manufacturers' specifications are increasingly more demanding and exacting. Powder granulations processed using tablet presses or encapsulators must possess specific physical properties to ensure tableting and encapsulating operations function correctly and quickly. These properties are critical because production rates for high-speed presses range from 2,500 to 10,000 tablets per minute and for encapsulators, 1,000 to 1,500 capsules per minute. Technical and economic concerns are vitally dependent on problem-free granulations.

Companies worldwide are taking a hard look at the way they conduct their business to uncover ways to improve both the quality and the quantity of their products and services. Pradhan and Bhalariao [1] indicated that Hindustan Antibiotic Ltd. (HAL) now employs roller compaction technology instead of granulating technology. Compaction technology has improved HAL's per capita production by more than three times. They consistently aim to reduce antibiotic manufacturing overhead costs by increasing individual and overall productivity. These efforts are achieved by simplification of day-to-day operations and by modifying old procedures.

## A. Direct Compression

In solid-dosage manufacturing, direct compression process technology is the most effective and efficient way to make powder materials suitable for tableting or encapsulating without a step to increase particle size. Usually, an active drug substance is blended with directly compressible excipients such as Avicel, Starch 1500, Emdex, or lactose to form a homogeneous mixture, which is then directly compressed or encapsulated into tablets or capsules. The key powder blend properties required to manufacture directly compressible tablets and fill hard gelatin capsules are

- Good powder cohesiveness
- Good granule flow characteristics
- Narrow particle size range
- Minimum granule segregation

When these key powder blend property features do not exist or cannot be developed in an economic or technical manner through direct compression, then, dry compression granulation technology can be used as an alternative process to enhance powder properties.

## B. Compression Granulation Technology

Compression granulation technology consists of two methods: slugging and roll compaction. The primary focus of this chapter is about roller compaction technology and its properties.

### 1. Slugging

Slugging consists of dry-blending excipients with an active drug substance and compressing the powder or powder blend into a large tablet or (slug) on a compressing machine. Large-diameter tooling, usually flatface 2.5 cm (1 in.) or more, is used to make the slugs. This compression setup, in turn, maximizes the slugging throughput, and minimizes the hopper feed-frame and die powder flow problems associated with the process. Slugging compression is normally performed at 4–6 tons pressure, at a rate of 10–30 turret revolutions per minute. The specific machine tonnage and dwell time required are dependent on the powder blend's physical properties and ultimately the slug specifications. After the slugs are formed, they are usually stored in process containers until they are needed to be sized for final blending and tableting requirements. There are numerous disadvantages with the slugging compression process:

- Single-batch process
- More maintenance  
overs
- Poor economies of  
low yield
- Low throughput per
- Poor process control
- Excessive support s  
quirements

### 2. Roller Compaction

Unlike the slugging method, properties as earlier described, are. Roller compaction technology control and a quality product. Its

- Simplifies processing
- Eliminates aqueous  
vent granulating
- Reproduces consisten  
lometry and density
- Improves content un
- Facilitates powder fl
- Uses less energy to
- Requires less man  
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- Improves drug dosa  
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Roller compaction techn controls and efficiencies. Rol regulating compaction pressu features offer high levels of formed compact.

## C. Particle-Bonding Process

The process of dry granulation rely on interparticulate bond terized in different stages, wh

pression process technology is the powder materials suitable for tableting. Usually, an actively compressible excipients such as to form a homogeneous mixture, encapsulated into tablets or capsules. To manufacture directly compress-

ity features do not exist or cannot be achieved in a direct compression manner through direct compression. This technology can be used as an alternative.

## ology

There are two methods: slugging and roller compaction. This chapter is about roller compaction.

Tablets with an active drug substance are compressed into a large tablet or (slug) using tooling, usually flatface 2.5 cm. This compression setup, in turn, minimizes the hopper feed-frame with the process. Slugging compresses powder, at a rate of 10–30 machine tonnage and dwell time. The drug's physical properties and ultimate strength are formed, they are usually needed to be sized for final blend. Numerous disadvantages with the

- Single-batch processing
- More maintenance changeovers
- Poor economies of scale and low yield
- Low throughput per hour
- Poor process control
- Excessive support system requirements
- Poor ergonomics
- Excessive air and sound pollution
- Excessive logistics
- Increase storage containers and space
- More energy is required to produce 1 kg of slugs than to produce 1 kg of roller compact

## 2. Roller Compaction

Unlike the slugging method, materials not exhibiting the key powder properties as earlier described, are well suited for the roller-compacting process. Roller compaction technology plays an important role in providing cost control and a quality product. Its process benefits are the following:

- Simplifies processing
- Eliminates aqueous and solvent granulating
- Reproduces consistent granulometry and density
- Improves content uniformity
- Facilitates powder flowability
- Uses less energy to operate
- Requires less manpower to operate
- Produces a dry product
- Improves drug dosage weight control
- Uses less raw materials
- Eliminates water-induced degradants
- Produces good disintegration tablets and capsules
- Does not require explosion-proof room and equipment
- Improves cycle time
- Prevents segregation
- Facilitates continuous manufacturing system

Roller compaction technology is a continuous process that offers better controls and efficiencies. Roller compactors are fitted with control devices regulating compaction pressure, roll speed, and powder feed speed. These features offer high levels of process control, throughput, and a quality formed compact.

## C. Particle-Bonding Process

The process of dry granulation technologies—slugging and compacting—rely on interparticulate bond formation. Granule bond formation is characterized in different stages, which usually occur in the following order: (a)

particle rearrangement, (b) particle deformation, (c) particle fragmentation, and (d) particle bonding.

When powder particles undergo an applied force or stress, a stress force is released from the granules, the granules attempt to return to their original shape or form; this is an *elastic deformation*. A deformation that does not totally recover after the stress is released is a *plastic deformation*. Both elastic and plastic deformations can occur simultaneously, but one effect usually predominates.

*Particle rearrangement* occurs initially as powder movement begins filling void spaces. Air begins to leave the powder blend's interstitial spaces, and particles begin to move closer together, thereby increasing the powder blend's density. Particle shapes and sizes are key factors in the rearrangement process. Spherical particles will move less than other-shaped particles because of their closer initial packing. Particle deformation occurs as compressional forces are increased. This deformation increases the points of contact between particles where bonding occurs and is described as plastic deformation.

*Particle fragmentation* is the next stage of bonding formation. It happens at higher compressional force levels. Here, particle fracturing creates multiple new surface sites, additional contact points, and potential bonding sites. *Particle bonding* occurs when plastic deformation and fragmentation happen. It is generally accepted that bonding happens at the molecular level, and this is due to the work of van der Waals forces.

Parrot [2] identifies that three theories of compressional bonding exist: mechanical, intermolecular, and liquid-surface film. Mechanical-bonding theory purports that individual particles undergo elastic, plastic, and brittle deformation. Bonding occurs because particle edges intertwine, forming mechanical bonds. Intermolecular theory identifies that there are some unsatisfied surface ions that have a potential need to bond to one another. Under pressure, intermolecular forces become pushed together close enough so that van der Waals forces can act to consolidate particles.

The liquid-surface film theory identifies that bonding occurs because of a thin liquid film. The thin liquid film is generated from pressure induced by the energy of compression. This, in turn, acts as a bonding agent promoting mechanical strength and an enlarged particle [2].

#### D. Current Industry Practices

A 1993 industrial survey [3] evaluated current pharmaceutical technology practices and preferences of innovator and generic U.S. drug manufacturers. The authors found that direct compression formulation is the process technology of choice for tablet manufacturing, followed by wet-massing gran-

ulation technology (fluid bed). It was indicated that about one-third of manufacturers recommend direct compression because of long lead times and the difficulty of commercialization and the uncertainty of the market. Companies would prefer granulation over direct compression if the formulator's rationale for product development is based on past experiences and successes. Of the manufacturers, 40% of nonprescription companies use roller compaction technology. Innovator companies use roller compaction technology as almost the least preferred technology as almost the least preferred technology received a lower preference score than the same questionnaire, and roller compaction is the least preferred technology on the list.

The surveyors' intention was to determine manufacturing respondents' current attitudes, policies, and preferences for roller compaction technology. There was no apparent reason to determine why these attitudes exist from a pharmaceutical industry perspective. Manufacturers need to determine why these attitudes exist. Second, they need to determine if roller compaction technology compared with other technologies. Manufacturers need to determine if roller compaction technology is and to improve formulators' attitudes toward roller compaction in the United States.

## II. PRINCIPLES OF COMPACTION

The principles of compaction design and operating parameters are used in a manner to produce an optimum compact.

The compact is further processed into the most important state, into finished product. The following principles and relationships are used in compaction:

- Screw feed
- Roll speed
- Roll pressure

deformation, (c) particle fragmentation, go an applied force or stress, a stress the granules attempt to return to their *elastic deformation*. A deformation that stress is released is a *plastic deformation*. These can occur simultaneously, but one ef-

Initially as powder movement begins in the powder blend's interstitial spaces, together, thereby increasing the powder particle sizes are key factors in the rearrangement. Particle deformation occurs as compression deformation increases the points of contact and is described as plastic

Next stage of bonding formation. It happens at three levels. Here, particle fracturing creates new contact points, and potential bonding occurs through plastic deformation and fragmentation. Bonding happens at the molecular level, through Van der Waals forces.

Theories of compressional bonding exist: surface film. Mechanical-bonding granules undergo elastic, plastic, and brittle deformation. Particle edges intertwine, forming mechanisms that identify that there are some unsatisfied bonds that need to bond to one another. Under pressure, particles pushed together close enough so that they weld together.

Identifies that bonding occurs because pressure is generated from pressure induced deformation. In turn, acts as a bonding agent produced by a deformed particle [2].

Current pharmaceutical technology and generic U.S. drug manufacturers. The primary formulation is the process technology, followed by wet-massing gran-

ulation technology (fluid bed then tray-drying methods). The survey indicated that about one-third of the innovator drug companies do not use or recommend direct compression technology. The authors [3] suggested that because of long lead times from active drug substance discovery to commercialization and the uncertainty of drug properties, the innovator companies would prefer granulation technology of one type or another. The formulator's rationale for process selection was based on past formulation experiences and successes. On the other hand, the generic, vitamin, and nonprescription companies overwhelmingly preferred direct compression technology. Innovator companies who responded to the survey, who used roller compaction technology in tablet manufacturing, identified the technology as almost the least preferred on average. Only all-in-one processing received a lower preference on average. Generic companies, who responded to the same questionnaire, rated the roller compaction technology as the least preferred technology on average.

The surveyors' intentions were to determine the pharmaceutical manufacturing respondents' current process technologies and their formulators' current attitudes, policies, and preferences for solid-dose-processing technology. There was no apparent attempt by the authors or questionnaire to determine why these attitudes and preferences exist. It now appears that, from a pharmaceutical industry viewpoint, roller compactor equipment manufacturers need to determine why certain process technology preferences exist. Second, they need to amplify the advantages of roller compaction technology compared with other technologies. Third, the equipment manufacturers need to determine what specific actions are necessary to change and to improve formulators' preferences for roller compaction technology in the United States.

## II. PRINCIPLES OF COMPACTION

The principles of compaction are based on the fundamentals of equipment design and operating parameters that influence the starting material in a manner to produce an optimum compact.

The compact is further handled through reduction to its ultimate and most important state, into free-flowing granules. In this section, key operating principles and relations are identified in context of the effects of compaction:

- Screw feed
- Roll speed
- Roll pressure

- Roll design
- Vertical feed screw versus horizontal feed screw
- Raw material delivery system
- Vacuum deaeration versus nonvacuum deaeration

Vacuum deaeration concepts are discussed later in the chapter. The significant effects of compaction are identified as particle size distribution, powder bulk density to compacted bulk density, compact hardness versus tablet disintegration and dissolution, recompression properties, compact tensile strength to granule size, and recirculation of fines.

### A. Operating Principles

Work accomplished by Cohn and co-workers [4], in the early 1960s, identified key compactor-processing variables to produce optimum potassium chloride tablets as amperage and raw material fines.

The initial trial responses indicated that the primary-compacting factors were motor amperage, and percentage fines. It was observed that as the effective raw material throughput increased, more power was required. One of the major difficulties of the compacting process was leakage of powders between the roller seals, as less material was brought in contact with the seals, less was forced through without being compacted. This effect is described as percentage fines. This is the amount of powder that goes through the compactor rolls without being compacted. It was the authors' opinion that a better fit of the compactor rolls and seals occurred when higher oil pressure was applied to the rolls; in turn, this produced less fines. During the trials, the authors recycled the fines into the raw material and did not subsequently observe negative tableting results. However, they did not report the quantity of fines collected versus the quantity of compact collected, nor the percentage quantity of fines put back into the starting material [4].

### B. Optimizing Variables

Optimization of compactor process variables to produce optimum compression granulations is vital to the formulating scientist. This is best achieved by understanding compactor parameter influences on product characteristics. It requires experience in handling active drug substances, experience in solid-dose formulation, and experience in process technology and handling roller compactors.

Typical roller compactor variables studied at high-, medium-, and low-force levels are (a) roll speed, (b) feed screw speed, and (c) roll pressure.

Falzone et al. [5] attempted to develop a general mathematical model relating roller compactor dimensions, compactor settings, and material char-

acteristics to predict optimum compaction. Their work was unsuccessful in determining a mathematical model for microcrystalline cellulose excipients. The effects of the compactor dependent variables on the characteristics of the material were not fully understood.

These scientists [5] modified the compactor settings for tablet recompressibility properties. They varied the following compactor parameters: roll speed, rate, horizontal feed rate, and pressure.

For Avicel PH 101, Falzone et al. [5] studied the effect of screw speed and the roll speed on the compaction characteristics. The roll speed was varied from 10 to 100 rpm. The amount and dwell time of the material in the compactor plastic-deforming material, is a function of the roll speed. This parameter determines the bulk density of the material and its effect on particle size.

For lactose, all three compactor parameters were studied. The compaction characteristics. The compaction characteristics of horizontal feed screws before and after compaction. The material as well as the roll separation. In summary, the significant parameters were the horizontal feed screw speed, roll speed, and pressure.

For the acetaminophen tablets, the compaction characteristics were significantly effected changes in the material. The material undergoes deformation by the compactor. The screws significantly interact with the material. The blend, thereby changing the material. The material is sensitive to compaction dwell time.

### C. Instrumentation Principles

Jerome et al. [6,7] evaluated the compactor process variables to produce optimum compacts. Their findings indicated that pressure was a more important factor as the pressure (rpms) in relation to roll speed. The compactor was fitted with strain gauges to measure the force signals. The force signals were amplified and recorded on a speed recorder. During the trial, the compactor speed over a wide rpm range as well as the pressure range was also widely adjusted.



vertical feed screw

vacuum deaeration

discussed later in the chapter. The material was characterized as particle size distribution, bulk density, compact hardness versus compression properties, compact tensile strength, and percentage of fines.

Wong [4], in the early 1960s, identified factors to produce optimum potassium permanganate granules.

He identified the primary-compacting factors as roll speed, roll pressure, and roll separation. It was observed that as the roll speed increased, more power was required. One problem with the process was leakage of powders from the compaction area. This was brought in contact with the roller. This effect is due to the dwell time of powder that goes through the compaction area. It was the authors' opinion that leaks occurred when higher oil was used. This produced less fines. During the process, the raw material and did not compact. However, they did not report the quantity of compact collected, nor the percentage of compact to the starting material [4].

Wong et al. [4] produced optimum compacts. This is best achieved by varying the roll speed, roll pressure, and roll separation on product characteristics. For drug substances, experience in compaction process technology and handling

was studied at high-, medium-, and low-roll speeds, and (c) roll pressure. A general mathematical model for compaction factor settings, and material char-

acteristics to predict optimum roller compactor settings. Their work was unsuccessful in determining a general statistical model for lactose and microcrystalline cellulose excipients and acetaminophen drug blend: the actual effects of the compactor depended more on the bonding and deformation characteristics of the material that was roller compacted.

These scientists [5] monitored particle size distribution changes and tablet recompressibility properties of the roller-compacted granulations. They varied the following compactor parameters at differing speeds: roll rate, horizontal feed rate, and vertical feed rate.

For Avicel PH 101, Falzone et al. [5] found that the horizontal feed screw speed and the roll speed had the greatest influence on granulation characteristics. The roll speed and horizontal feed screw controlled the amount and dwell time of the material in the compaction area. Avicel, a plastic-deforming material, is significantly influenced by dwell time. This parameter determines the behavioral characteristic of the Avicel-binding property and its effect on particle size and granule compressibility.

For lactose, all three compactor variables effected changes in granulation characteristics. The compressibility was affected by the vertical and horizontal feed screws before compaction. The density of the incoming material as well as the roll separation affected the lactose compaction conditions. In summary, the significant compactor variables for this evaluation were the horizontal feed screw speed and the roll speed.

For the acetaminophen drug blend, all three compactor variables significantly effected changes in the granulation characteristics. Acetaminophen undergoes deformation by brittle fracture. The vertical and horizontal feed screws significantly interacted in the deformation of the acetaminophen blend, thereby changing the granulation behavior. The material was also sensitive to compaction dwell time [5].

### C. Instrumentation Principles

Jerome et al. [6,7] evaluated compactor adjustments to determine how to produce optimum compacts. They identified key-operating parameters. Their findings indicated that pressure applied to the movable roll was not as important a factor as the precompactor feed screw revolutions per minute (rpm) in relation to roll speed rpm. In additional studies, a roller compactor was fitted with strain gauges measuring forces applied to the fixed roll [8]. The force signals were amplified and observed on an oscilloscope and high-speed recorder. During the trials the precompactor feed screw was adjusted over a wide rpm range as well as the roll speed. The compacting roll pressure range was also widely adjusted.

The resultant force was measured from the applied roll pressure and the resistance of the different powders pushed by the precompactor feed screw. For a given powder, the resistance varied according to the amount of the powder fed by the screw at a given roll speed.

Jerome et al. [8] showed compaction profiles relating the resultant measured compaction force over 2- to 3-min continuous compaction periods. The apparent profiles demonstrated 25- to 30-s ramping-up force measurements before the force signals gave a consistent signal pattern. The force pattern remained repeatable until the last 15–25 s of the compaction process. At this point, lower force readings were observed owing to reduced powder quantities going through the system.

Good powder compaction profiles using lactose demonstrated repeatable force patterns over the operating times. Force amplitude variability, peak to draw, measured 15–20% of the total observed compacting force peak. On the other hand, corn starch, a poor-flowing powder, exhibited repeatable force patterns. However, the force amplitude variability measured 75% of the total observed compacting force peak. Jerome et al. [8] showed that different roll configurations give different resulting force measurements when compacting the same material under identical conditions. This is partly because the powder resistance depends on the shape of the compactor roll pockets.

Additional trials evaluated the effect of different roll pressures [8]. They compacted Elcema G 250, and adjusted the roll pressure to 120 and 150 bars, while holding constant the roll and the feed screw speeds. They observed no significant force measurement differences between the two compaction profiles. When the roll pressure was kept constant and the precompactor feed screws were set at two different speeds, substantially different force readings were measured. Expanding this latter test to lactose at three different feed screw settings, they observed a nonlinear relation between the speed and the force measured.

From a practical standpoint, the compaction instrumentation technology helped them during the development of two new tablet products. In one example, they measured the force compactability of a powder, with 30% water content, that demonstrated an ease of compaction, but difficulty in sizing. When the powder was dried to 14%, the compaction was difficult because of the heat generated and the excessive fines obtained during sizing. The instrumentation aided the scientists in selecting an intermediate powder moisture point that produced a compact that did not overheat, and that also sized easily and produced an acceptable range of fines.

A second example illustrated optimum feed screw speed settings and compaction pressure to improve tableting results. Jerome et al. [8] found that higher precompaction screw feed speeds and lower applied roll pressure

produced hard tablets superior with higher applied roll pressure. Compaction pressure and roll speed are an indirect measure of the process itself.

#### D. Overcompaction Principles

At a fixed roll speed, overcompaction of material powders can cause a variety of problems. Overcompaction can cause compact discoloration. Overcompaction may not be problematic in a sublingual or buccal pharmaceutical dosage form. Overcompaction or discoloration needs to be evaluated in terms of the compaction process. The following should be conducted:

1. Compact sizing
  - a. What is the size distribution?
  - b. How do these relate to capping?
  - c. Are there significant trends?
2. Final blend characteristics
  - a. What are the physical properties apparent density?
  - b. What type of effect?
  - c. Is there a color change?
3. Final dosage form
  - a. What is the physical appearance?
  - b. What are disintegrants?
  - c. What are the uniformity tests?

Assessing these issues (compact splits and compact strength) requires a design engineer to understand the process.

Hakanen and Laine [9] studied the effect of microcrystalline cellulose by varying the amount of chemical emissions during the compaction process. The intra was significantly different from the control. Excessive compaction force or overcompaction occurred. The authors

from the applied roll pressure and  
dictated by the precompactor feed  
varied according to the amount of  
speed.

profiles relating the resultant  
continuous compaction periods.  
30-s ramping-up force measure-  
consistent signal pattern. The force  
-25 s of the compaction process.  
observed owing to reduced powder

ing lactose demonstrated repeat-  
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peak. Jerome et al. [8] showed  
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identical conditions. This is partly  
the shape of the compactor roll

of different roll pressures [8].  
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t speeds, substantially different  
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a nonlinear relation between the

compaction instrumentation technol-  
two new tablet products. In one  
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in feed screw speed settings and  
results. Jerome et al. [8] found  
s and lower applied roll pressure

produced hard tablets superior to the combination of lower screw feed rates  
with higher applied roll pressures. The level of forces measured during the  
compaction are an indirect measurement of the energy developed during  
compaction. The energy observed is the resultant of all the force parameters  
of the process itself.

#### D. Overcompaction Principles

At a fixed roll speed, overcompaction with high roll pressure on starting  
material powders can cause a splitting of a compressed compact and even  
cause compact discoloration. These observed process conditions may or may  
not be problematic in a subsequent pharmaceutical process step or final  
pharmaceutical dosage form. The severity of the compact capping, splitting,  
or discoloration needs to be evaluated in terms of the total process, not just  
in terms of the compaction process step. The following process evaluations  
should be conducted:

1. Compact sizing
  - a. What is the sizing behavior, milling conditions, particle size distribution?
  - b. How do these parameters compare with or without compact capping?
  - c. Are there significant differences in compression characteristics?
2. Final blend characteristics
  - a. What are the physical blend characteristics; angle of repose, apparent density, flow, and so forth?
  - b. What type of excipients are added and for what reasons?
  - c. Is there a color blend uniformity issue?
3. Final dosage form
  - a. What is the physical appearance of the dosage form?
  - b. What are disintegration and dissolution profiles?
  - c. What are the uniformity, assay, and degradant values?

Assessing these issues in terms of the overcompaction phenomenon  
(compact splits and compact discoloration) enables the formulator or process  
design engineer to understand and determine proper compactor settings.

Hakanen and Laine [9] studied the overcompaction phenomena of mi-  
crocrystalline cellulose by varying the roll pressure and measuring the acous-  
tical emissions during the compaction process. The acoustical emission spec-  
tra was significantly different between normal compaction force and  
excessive compaction force when compact splitting (capping) and discol-  
oration occurred. The authors demonstrated, using microphones, that they

were able to separate the frequency components. This enabled them to capture information about physical phenomena related to powder compaction behavior. They used the information to predict, adjust, and control the compaction process. The integration of the acoustical power appeared to make possible the quantitative analysis of the capping phenomenon as a function of the applied compression force.

## E. Compaction Principles

### 1. Acoustical Characterization

Powder compaction is partly based on the fact that van der Waals forces are able to cause binding between particles at close distances. Bonding improves if the number of connection points between powder particles increases. The closeness of particles and the number of connection points are two important factors in powder binding.

During powder compaction, friction and particle fracture give off acoustical emissions. These sounds are produced primarily in an audible region, which can yield information about compaction behavior and pharmaceutical materials in use.

Hakanen and Laine [10] also studied and recorded acoustical emission measurements of lactose monohydrate, microcrystalline cellulose, and maize starch during compaction. The acoustical emissions were recorded for the excipients compressed at different kilonewton (kN) forces. The acoustical emissions were transformed to frequency spectra. They observed that the roller compactor-operating sounds produced discrete frequency peaks. The sounds produced from the compacting powders appeared on wider frequency bands. The roller compactor sound frequencies did not change as the compression forces varied.

Their findings indicated that the maize starch produced the largest single audible band. They concluded that this was due to the starch's ability to pack. Hakanen et al. [10] observed the most unique compaction characteristics occurring in the higher kilohertz region. Lactose monohydrate and microcrystalline cellulose were better compacted at higher forces 20–30 kN. They speculated that the shape and strength of these two raw materials were the reasons that it took higher forces to achieve the improved compacts. Microcrystalline cellulose demonstrated unique audible peaks occurring at 30 to 40 kN force. The compact was also observed to split into two parts, indicating a capping phenomenon.

### 2. Roll Speed

What is the optimum roll speed? What factors does the formulating scientist need to consider to maximize compact quality and compaction throughput?

Johanson [11] attempted to analyze the effect of roll speeds for briquetting presses. He considered even the gas and liquid phases that could be released from a solid mass. Solid properties were evaluated to predict the quality of the briquette for a constant quality briquette. His work showed the relationship between roll speed and the essentially proportional to the initial powder was compacted. As the roll speed and permeability increased; however, the roll speed and the compression force decreased, and the roll speed decreased significantly. Johanson's work showed that if the feed pressure is kept constant and the roll speed is increased, the pressure applied to the briquette will decrease. As a consequence, the briquette density will decrease.

### 3. Deaeration

Roller compaction deaeration is a topic that will be discussed in section IV.F.

## III. ROLLER-COMPACTED POWDERS

### A. Bulk Density and Flowability

The key effect of compaction is on the powder flow properties. A powder's flow properties change during storage and handling. The pharmaceutical manufacturing personnel, pharmaceutical scientists, and this type of powder behavior are the result of compaction experiments with actual powders. The density ratio increases as the compaction force increases. It showed that the bulk density of the powder increased 50 to 200% more than the original bulk density. There was little effect in improving the powder's flowability. When hydrous lactose was used, the flowability was very flowable materials. The powder stopped during funnel hopping. The two products' flowability was the same. The relation between bulk density and the amount of calcium and magnesium carbonate was the same.

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Johanson [11] attempted to answer these questions by predicting limiting roll speeds for briquetting presses. He developed mathematical expressions considering even the gas and liquid effects as they can theoretically be squeezed from a solid mass. Solid properties, press dimensions, and operating conditions were evaluated to predict optimum roll speeds. The results necessary for a constant quality briquette are most critical for low-density fine particles. His work showed the relation between feed pressure and roll speed to be essentially proportional to the material's permeability. For example, when the initial powder was compacted, sized, and recompactd, the bulk powder permeability increased; however, when the powder was recompressed, the compression force decreased, and the compactor feed pressure force requirement decreased significantly. Johanson [11] also demonstrated that if the compactor feed pressure is kept constant and the press speed is increased, the maximum pressure applied to the briquette decreases as the roll speed increases. As a consequence, the briquette density and strength decrease likewise.

### 3. Deaeration

Roller compaction deaeration concepts and principles are discussed in Section IV.F.

## III. ROLLER-COMPACTED POWDER PROPERTIES

### A. Bulk Density and Flow

The key effect of compacting is to increase bulk density and to improve powder flow properties. A powder with poor flowability typically consolidates during storage and handling or exhibits flow discharge problems. Manufacturing personnel, pharmaceutical scientists, and engineers do not want this type of powder behavior for many reasons. Parrott [12] conducted compaction experiments with active drug substances and excipients to compare the density ratio increases under increasing compaction pressures. He showed that the bulk density of some compacted materials increased from 50 to 200% more than the original bulk density. In some instances, there was little effect in improving the flowability of these powders. The investigation also showed that not all materials can be compacted to improve flowability. When hydrous lactose and granular dicalcium phosphate, which are very flowable materials, were compacted and sized, their flowability stopped during funnel hopper flow experiments. The compaction destroyed the two 'products' flowability. Parrott [12] demonstrated a linear relation between bulk density and the logarithm of compaction pressure for calcium and magnesium carbonates.

## B. Polymers

Roller compaction technology studies conducted by Sheskey et al. [13] evaluated hydrophilic polymers (methycellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and polyvinyl pyrrolidone) pregelatinized corn starch, and microcrystalline cellulose as dry binders to manufacture immediate-release niacinamide tablets. The parameters studied were

- Different polymers and concentrations
- Different roller pressure levels
- Granule hardness
- Tablet physical characteristics: hardness and friability
- Dissolution and disintegration profiles

Sheskey et al. [13] found that the tablet dissolution rate was dependent on binder concentration and independent of applied roller pressure in samples containing methylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), and polyvinyl pyrrolidone (PVP) binders. They also noted that the binder level did not affect the dissolution rate of tablets containing pregelatinized corn starch and microcrystalline cellulose.

In general, their findings indicated that higher binder levels produced better tablet physical properties, increased crushing strength, and decreased friability. At higher roll pressure levels, tablets were produced with poorer tablet physicals: decreased hardness and increased friability.

## C. Different Technologies

Mollan and Celik [14] used three differently manufactured maltodextrin excipients to determine their effect on tablet properties. The maltodextrin excipients evaluated were spray granulated, fluid bed agglomerated, and roller compacted. These excipients were studied for powder properties and post-tableting characteristics during the manufacture of propranolol hydrochloride tablets. The parameters examined were

- Loss on drying
- Surface area
- Density
- Flowability
- Compressibility index
- Tablet crushing strength versus applied force
- Disintegration times versus applied pressure
- Dissolution times versus applied pressure
- Friability values versus maximum applied pressure
- Brittle fracture versus plastic-elastic deformation

The studies also included other filler-binder excipient comparisons: hydrous

lactose USP, hydrated dextrate, USP.

The roller-compacted materials had smaller pores and more large, dense pores, or the fluid bed agglomerated materials inhibited the highest bulk and tapped densities. It showed that high bulk-density materials have low-flowability.

The tablet disintegration times showed relatively no disintegration time differences in range studies. Furthermore, the values and disintegration times were not affected. The maltodextrins disintegration times were not affected by porosity or bonding effects. The limiting (gel) layer that formed on the surface of Flo lactose excipient tablets did not affect disintegration.

The roller-compacted materials showed different behavior, whereas the other materials showed different forming characteristics. Dissolution and compression forces, indicated by the disintegration results in the tablets [14].

## D. Reworkability

In general, to make hard free-flowing process and to obtain an acceptable careful process evaluation and control.

Malkowska and Khan [15] studied the effect of roller compaction on the reworkability of a compacted granule. This reduction was more significant at higher pressures. The reworking is attributed to the reduction of robust granules. The lattice dislocations. These structural deformation compared to the initial state.

Malkowska et al. [15] studied the effect on tablet porosity but not on the strength. These results were observed in the directly compressible Starch 1500. The reworkability was also observed when

ducted by Sheskey et al. [13] evaluated hydroxypropylmethylcellulose, pyrrolidone) pregelatinized corn dry binders to manufacture immediate-release tablets. Parameters studied were

tations

hardness and friability profiles

Tablet dissolution rate was dependent on the level of applied roller pressure in samples containing hydroxypropylmethylcellulose (HPMC), polyvinyl pyrrolidone (PVP) binders. Roller pressure did not affect the dissolution rate of samples containing microcrystalline cellulose. Samples with higher binder levels produced tablets with increased crushing strength, and decreased friability. Tablets produced with poorer friability.

Tablets manufactured with maltodextrin excipients showed different properties. The maltodextrin excipients were fluid bed agglomerated, and roller compaction was used for powder properties and post-compaction structure of propranolol hydrochloride

- Disintegration times versus applied pressure
- Dissolution times versus applied pressure
- Friability values versus maximum applied pressure
- Brittle fracture versus plastic-elastic deformation

Inter excipient comparisons: hydroxy

lactose USP, hydrated dextrans NF, and dibasic calcium phosphate dihydrate, USP.

The roller-compacted maltodextrin excipient powder had fewer large pores and more large, dense, and rough surface areas than the spray-dried or the fluid bed agglomerated materials. The roller compacted excipient exhibited the highest bulk and tap densities. Their powder flow analyses showed that high bulk-density materials have high-flow rates, and low-bulk density materials have low-flow rates [14].

The tablet disintegration times containing maltodextrin excipients had relatively no disintegration time differences throughout the compression range studies. Furthermore, there was no correlation between crushing force values and disintegration times above 75 Mpa applied compression force. The maltodextrins disintegration behavior was not controlled by tablet porosity or bonding effects. The disintegration rate was controlled by a rate-limiting (gel) layer that formed around the tablet during disintegration. Fast-Flo lactose excipient tablets demonstrated faster disintegration times [14].

The roller-compacted material demonstrated a higher degree of brittle behavior, whereas the other maltodextrins all exhibited plastic-elastic deforming characteristics. Dissolution trials, at three different applied tablet compression forces, indicated that the roller-compacted maltodextrin excipient had dissolution results indistinguishable from those of other maltodextrins [14].

#### D. Reworkability

In general, to make hard free-flowing granules during a compaction or slugging process and to obtain an optimized powder blend for tableting requires careful process evaluation and consideration.

Malkowska and Khan [15] showed that reworking a powder blend is influenced by the compaction behavior of the excipients. When they recompressed a compacted granulation, generally it reduced the tablet strength. This reduction was more significant when the initial compaction was carried out at higher pressures. The reduction of tablet tensile strength on tablet reworking is attributed to the granules' work-hardening effect and the production of robust granules. This effort is due to the high level of crystalline lattice dislocations. These strong granules have increased resistance to additional deformation compared with noncompacted granules.

Malkowska et al. [15] found that recompressing appears to have no effect on tablet porosity but does have a direct effect on tablet strength. These results were observed with plastic-deforming Avicel PH 102 and directly compressible Starch 1500 and Emcompress excipients. This phenomena was also observed when compacting and directly compressing various

fractional blends of microcrystalline cellulose and dicalcium phosphate. The authors also noted that granules obtained from compacts that were initially compressed at intermediate pressure levels produced stronger tablets than those prepared from granules obtained from high-pressure compacts.

### E. Microbial Load

Microbial control of pharmaceutical products is not meaningful if microbial control measures have not been evaluated throughout all phases of manufacturing and development, such as

- Product development
- Raw materials
- Manufacturing procedures
- Manufacturing environment
- Manufacturing equipment
- Packaging materials
- Packaging procedures
- Packaging environment
- Packaging equipment

Ibrahim [16] demonstrated that direct compression-tableting compression produced lower microbial levels than those tablets made by a wet granulation method. The compression process exerted lethal effects on microorganisms. These results indicated that tablet microbial levels were influenced by the starting raw materials' microbial quality, the production environment, and the processing technology.

Roller compaction-tableting studies evaluating microbiological survivability have not been published. Ibrahim's study provides potential application inferences and awareness of microbial contamination risks when manufacturing solid-dosage forms. Ibrahim [17] manufactured folic acid tablets by two process technologies: direct compression and wet granulation methods. The powder raw materials evaluated to determine the microbial load were: folic acid, corn starch, lactose, gelatin, polyethylene glycol 6000, distilled water, talc, magnesium stearate, microcrystalline cellulose, and dicalcium phosphate. The processing steps for both technologies are listed in Table 1. The microbiological plate counts and colonies were examined at each processing step to determine Gram reactions and pathogenic organisms. The highest microbial level was obtained at the wet granulation stage (five times greater than any other stage). The microbial load was attributed to the use of a highly contaminated binder solution.

Tablets manufactured by the direct compression method contained lower bacterial and fungal counts than those produced by the wet granulation method. The microbial levels of the granules produced from both processes were reduced during tablet compression. The greatest microbial percentage reduction occurred from the direct compression granules. Ibrahim [18] suggested that the microbial count reductions could be attributed to the follow-

**Table 1** Manufacturing Processes

Direct compression

Size ingredients

Ball mixer blend (all ingredients)

Compress

ing mechanisms: (a) no water, (b) no equipment to contaminate, (c) no thermal microbial killing, (e) oxygen starvation.

### F. Binder Distribution

Roller compaction relies on granule rearrangement, plastic deformation, granule properties and undersize distribution are important to obtain optimum granule size and fragmentation are considered. On the other hand, elastic deformation and hardness [19].

Seager et al. [20] evaluated the effect of roller compaction, wet massing, and process technologies and mechanical properties of products vary. All of the granules were solvated, identifying the binder distribution and gelatin-type binder. After granulation, the binder were solvated, identifying the binder distribution and gelatin-type binder.

The photomicrographs of the granules showed different ways in the granules.

Roller compacted: binder distribution

Wet massing: binder distribution (network)

Spray drying: high local binder distribution



lucose and dicalcium phosphate. The tablets from compacts that were initially produced produced stronger tablets than from high-pressure compacts.

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ed throughout all phases of manu-

- Packaging materials
- Packaging procedures
- Packaging environment
- Packaging equipment

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process exerted lethal effects on mi-  
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evaluating microbiological survival. This study provides potential application contamination risks when manufacturing [7] manufactured folic acid tablets. Compression and wet granulation methods were used to determine the microbial load of microcrystalline cellulose, polyethylene glycol 6000, and disintegrants for both technologies are listed in Table 1. Counts and colonies were examined at various stages and pathogenic organisms. The results at the wet granulation stage (five tablets) showed that the microbial load was attributed to the wet granulation process.

compression method contained the product produced by the wet granulation. The granules produced from both processes were similar. The greatest microbial percentage was found in the compression granules. Ibrahim [18] suggested that this could be attributed to the following factors:

**Table 1** Manufacturing Processing Steps

Direct compression	Wet granulation
Size ingredients	Size ingredients
Ball mixer blend (all ingredients)	Ball mixer blend (starch and active)
Compress	Binder solution preparation
	Wet granulate (above with gelatin and distilled water binder solution)
	Dry mass, 2 h, 50°C
	Size dried mass
	Ball mixer blend (all ingredients)
	Compress

ing mechanisms: (a) no water contamination, (b) fewer process steps and equipment to contaminate, (c) less manufacturing time to contaminate, (d) thermal microbial killing, (e) pressure microbial killing, and (f) aerobic oxygen starvation.

## F. Binder Distribution from Different Technologies

Roller compaction relies on powder bonding mechanisms such as particle rearrangement, plastic deformation, and particle fragmentation. Determining granule properties and understanding how to control the compaction process are important to obtain optimum tablet hardness. Particle plastic deformation and fragmentation are considered to have a positive effect on tablet strength. On the other hand, elastic deformation usually has a negative effect on tablet hardness [19].

Seager et al. [20] evaluated paracetamol granulations produced by roller compaction, wet massing (planetary mixer), and spray drying. The process technologies and mechanisms are different, and the properties of the products vary. All of the granulation premixes contained the same quantity and gelatin-type binder. After granulation, the active drug–binder masses were solvated, identifying the binder matrix system structure.

The photomicrographs showed that the binder was distributed in different ways in the granules. Characterization is as follows:

**Roller compacted: binder distributed a limited number of points**

Wet massing: binder fairly evenly distributed throughout the granule (network)

**Spray drying: high local concentration at the granule surface**

The granulations were tableted. The roller-compacted granulations gave the lowest tablet mechanical hardness. Wet massing gave an intermediate strength, and the spray-dried tablets resulted in the highest mechanical hardness. The high local concentration of the binder at the granule surface suggested that this method provided the best-binding capability. To improve the dry granulation binder distribution, it appears that the binder material needs to be finely divided and uniformly distributed. In effect, this means a milling and preblending step would help distribute the finely divided binder effectively throughout the mixture before the compaction step.

In summary, the different results were due to the different binder distributions in the granulated masses. Seager et al. [20] concluded that the binder located nearest the granule surface was most effective in increasing tablet mechanical hardness. In effect, the increased intergranular bonding caused increased tablet hardness.

From additional studies Seager et al. [21,22], in a series of publications, describe how the granule manufacture and structure affect the disintegration and dissolution times. Roller-compacted tablets of the same porosity (as those tablets manufactured by wet massing and spray granulation technologies), produced comparable or better tablet disintegration and dissolution profiles. This was attributable to the bonding characteristics of the roller-compacted product. Also, in this study, the roller-compacted tablets produced were soft with poor hardness properties.

### G. Tablet Disintegration and Dissolution

Chalmers and Elworthy [23] assessed granule and tablet properties when using two different processes to manufacture oxytetracycline dihydrate tablets (OTC). The trials incorporated microcrystalline cellulose and alginic acid with OTC. Tablets made from wet granulating with water and polyvinyl pyrrolidone solution, and with water alone were compared with tablets compressed from (slugged) granules. Tablets from slugged granules always disintegrated and dissolved faster than the same formulation prepared by the two wet granulation methods.

The authors [23] concluded that powders with different hydrophobicity and different degrees of surface roughness will differ in their ability to form crystalline bridges. Powder particles involved in such processes are likely to be moved to new positions when in contact with an aqueous medium. They hypothesized that the more hydrophobic particles will not enter so easily into the formulation of liquid-induced bonds during disintegration and dissolution testing. This additional nonhomogeneity was thought to explain why tablets made from granules, prepared by wet massing and screening, were slower to disintegrate and dissolve than those prepared from slugged material.

### H. Different Granulation Technologies

The purpose of the following comparison of granulation technologies (roller compaction vs. wet massing) was limited to two.

In trials agglomerating wet massed granules, it was found roller compaction to produce granules with better flow than the fluidized bed granulation. The roller-compacted granules exhibited a low degree of inhomogeneity. The roller-compaction process produced highly porous granules. The individual particles formed in the roller-compaction process exhibited better flow characteristics than the granules produced by testing in comparison with the granules produced by the granule bulk density had.

1. Granules formed by roller compaction have higher strength compacts than granules formed by wet massing. Compression pressure required to disintegrate the granules was lower for the roller-compacted granules.
2. Li et al. [23a] noted that granules subjected to great stress during compaction, therefore, the subsequent work-hardening of the granules. The work-hardening caused an increase in granule strength and a decrease in compact tensile strength.

### I. Controlled-Release Tablets

Sheskey et al. [24] conducted a study to evaluate the material flow properties of microcrystalline cellulose and magnesium stearate. By using a roller-compaction process, they successfully demonstrated the production of controlled-release tablets with niacinamide into free-flowing granules.

They also [24] compared the material flow properties of intermediate-, and high-compaction granules. The granules were selectively sized. The granules produced by the roller-compaction process attributes: recompaction and disintegration characteristics.

Evaluations of the selectivity of the granules were produced at low compaction pressures. The granules were produced at higher compaction pressures than observed in compacting powders.

the roller-compacted granulations. Wet massing gave an intermediate result in the highest mechanical strength at the granule surface and binder-binding capability. To improve the binder distribution, it appears that the binder material should be more uniformly distributed. In effect, this means a more uniform distribution of the finely divided binder throughout the compaction step.

Due to the different binder distribution, Li et al. [20] concluded that the roller compaction was most effective in increasing the intergranular bonding.

Li et al. [21,22], in a series of publications, have shown that the structure and composition affect the disintegration and dissolution of roller-compacted tablets of the same porosity. Wet massing and spray granulation affect tablet disintegration and dissolution characteristics of the tablets. In this study, the roller-compacted tablets showed improved properties.

## Conclusion

Granule and tablet properties when prepared by roller compaction of oxytetracycline dihydrate tablets with microcrystalline cellulose and alginic acid were compared with tablets compressed from slugged granules always disintegrated. The same formulation prepared by the

rollers with different hydrophobicity will differ in their ability to form tablets. The tablets prepared in such processes are likely to disintegrate with an aqueous medium. They will not enter so easily into solution. The disintegration and dissolution were thought to explain why tablets prepared by roller compaction and screening, were slower to disintegrate from slugged material.

## H. Different Granulation Technologies

The purpose of the following investigation was to study the effects of granulation technology (roller compaction versus fluid bed). The trial formulations were limited to two.

In trials agglomerating Maltrin M150 and Maltrin M550, Li et al. [23a] found roller compaction to produce granules with higher bulk density than the fluidized bed granulation method. The roller compactor densification exhibited a low degree of intragranular porosity, whereas the fluidized bed process produced highly porous granules. This was achieved through binding individual particles formed by crystalline bridges. The roller-compacted granules exhibited better flowability during gravimetric and volumetric flow testing in comparison with the fluidized bed granules. The granule size and the granule bulk density had a positive effect on the granule flow rate.

1. Granules formed from roller compaction exhibited lower tensile strength compacts than fluidized bed granules under a range of compression pressures.
2. Li et al. [23a] noted that the fluidized bed granules were not subjected to great stresses and deformation during their formation and, therefore, the subsequent compact maintained its compressibility. The work-hardened roller-compacted granules caused a significant increase in granule yield pressure and a pronounced decrease in compact tensile strength.

## I. Controlled-Release

Sheskey et al. [24] conducted studies to demonstrate the enhancement of material flow properties of niacinamide controlled-release matrix. The excipients used consisted of methylcellulose, hydroxypropylmethylcellulose, and magnesium stearate. By using roller compaction technology, the authors successfully demonstrated the processing of high molecular weight polymers with niacinamide into free-flowing granules that were compressed into controlled-release tablets.

They also [24] compacted prepared powder blends at low-, intermediate-, and high-compaction pressure levels, and collected compacts that were selectively sized. The granule portions were evaluated for the following process attributes: recompactability, content uniformity, and tablet characteristics.

Evaluations of the selective granule portions indicated that smaller granules were produced at lower compaction pressures and larger granules were produced at higher compaction pressures. This relation is typically observed in compacting powder blends. It is explained by higher compactor

pressures producing a stronger, more resilient powder mass which, when subsequently milled, resists sizing. This, in turn, produces a coarser particle size distribution.

Compressed tablets from the three different pressure compacts demonstrated consistently higher hardness values and lower friability results from granulations compacted at the lowest compaction pressures. These findings parallel other authors' results [25,26] pertaining to reworking compressed tablets into sized granules that were then recompressed into tablets.

Sheskey et al. [26] also found that extensive recycling of coarse and fine materials with the original feedstock produced poor tablet content uniformity results. The subsequent tablet compression produced lower tablet hardness values than were observed in the original tablet compression. This situation is explained by the production of robust granules that exhibit increasing resistance to deformation during recompression. This effect is known as the work-hardening principle.

Sheskey et al. [27] found no apparent relation between the compaction pressure level applied to the polymers in the matrix system and the resultant drug dissolution. Also no relation was observed between the tablet hardness levels and the resultant drug dissolution. In their studies, they observed that the granulation densities increased because of roller compaction.

Generally, the scientists experienced lower tablet dissolution profiles from recycled granules. They theorized that initial very low roller compaction pressure did not allow the drug and polymer to bond sufficiently. This physical situation may have permitted granule separation during the product recycling which also caused the nonuniform drug levels in the tablets [27].

## J. Sustained-Release

Roller compaction technology has been used to prepare sustained-release granules, rather than by organic solvent granulation processing. Kawashima et al. [28] prepared acetaminophen sustained-release granules using low substituted hydroxypropylcellulose (L-HPC) by compacting the mixture. The prepared granules were directly compressed into sustained-release tablets.

The physical mixtures were compacted at different pressures, and the tablets produced from these compacted mixtures yielded different drug release profiles and different tablet tensile strengths. The authors were able to control the drug release of the resultant tablets from rapid to sustained-release by changing the roller compaction pressure. The drug release profiles showed that granules produced at low compaction roll pressures demonstrated sustained-release properties. Granules prepared by high compaction roll pressures produced rapidly swelling and fast-dissolving tablets. The opposite was true for granules produced at low compaction pressures.

## Roller Compaction Technology

Kawashima et al. [28] related the granulation process to the swelling work of the granules. Granules produced at higher pressures were mechanically strong; therefore, they did not break individual granules into coarse particles. The median pore radius of the granules increased with the pressure. The penetration of air as the pore radius increased promoted the disintegration of the granules at compaction pressures.

## IV. ROLLER COMPACTION

Briquetting and compacting of powders into waffles or wafers obtains specifically defined shapes. Waffles are defined as compacted granules.

The basic principles of roller compaction are: material is fed into a counterrotating roll pair (Fig. 1). Both rolls are driven by a motor and the other roll axis is slightly offset.

Initially during the process, the powder is drawn near the roll pair surfaces and then compressed. The powder is drawn near the roll pair surfaces and then compressed. The powder is drawn near the roll pair surfaces and then compressed.

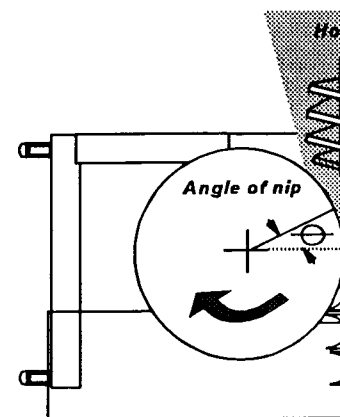


Fig. 1 Typical Compactor-feed system with a driven auger screw.

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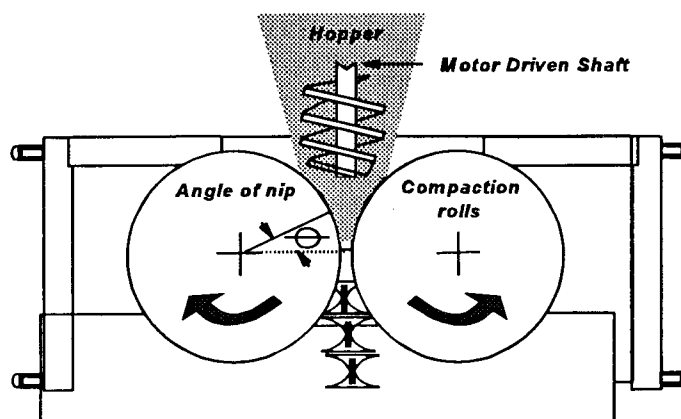
Kawashima et al. [28] related their observations to tablet size distribution and the swelling work of the granules produced under various pressures. Granules produced at higher compaction pressures were assumed to be mechanically strong; therefore, it was more difficult to destruct or crush the individual granules into constituent fine powders. The results indicated that the median pore radius of the tablet increased by increasing the compaction pressure. The penetration speed of the water into the tablet became faster as the pore radius increased. A rapid penetration of water into the tablet promoted the disintegration of tablets using granules prepared with higher compaction pressures.

#### IV. ROLLER COMPACTOR DESIGN

Briquetting and compacting are densifying techniques for dry powders. Briquetting obtains specifically shaped units. Compacting fragments, flakes, or waffles are defined as compaction of undefined sizes and shapes.

The basic principles of roller compaction begin when powdered material is fed into a counterrotating pair of rolls by gravity or by a force-feed screw (Fig. 1). Both rolls are fixed on their axes, or one roll has a fixed axis and the other roll axis is slightly movable.

Initially during the powder feed, the powder materials rub against the roll pair surfaces and then are drawn into the nip angle area. There the powder is drawn near the roll pair and begins to be predensified. The powder then feeds into the roll gap, where the particles are rearranged and densified



**Fig. 1** Typical Compactor-feeding system illustrating conical hopper with motor-driven auger screw.

and plastic deformation occurs [29]. The nip angle varies according to the physical properties of the feed powder and, to some degree, to the nature of the feeding mechanism and the physical characteristics of the rolls [30]. A compact is formed that is immediately sized for intended needs.

### A. Design History

Compactor design characteristics have evolved over the years. By the mid-1970s, research revealed a number of roll design improvements that increased compacting efficiency. Three key conditions were identified, at that time, which optimized the roll compact and minimized the leakage of uncompacted powder [30]:

1. Adequate powder supply must enter the gripping zone.
2. Powder must be conveyed fully into the narrowest part of the roller gap.
3. Compaction pressure must be distributed as uniformly as possible over the whole of the roller-gripped powder mass.

Equipment engineers and researchers worked on improving feeding equipment systems and roll designs to satisfy and maximize the foregoing conditions. Some of the key advances identified were [31] the following:

- Installing concavoconvex roll surface, rather than a flat roller pair
- Optimizing roll rim angle to  $65^\circ$
- Installing rectangular feed chute and flaps
- Designing cylindrical, conical-cylindrical, or tapered-shaped variable-speed auger feed screws
- Installing digital- and analog-variable feed screw controllers
- Developing horizontal and variable screw feed systems

### B. Design and Mechanics

The following factors affect the compact strength of a bulk solid material during roller compaction:

- |  |                     |
|--|---------------------|
| • Applied pressure   | • Particle size     |
| • Air entrapment within the powder                         | • Particle density  |
| • Roll dwell time  | • Type of binders   |
| • Powder void fraction (space into which air is compacted) | • Material moisture |

There is a maximum applied pressure for each solid material that, if

exceeded, will produce a low strength is caused by the extrusion of fines. Factors influencing roll compaction [32]:

- Material flow properties
- Material variability
- Material compressibility
- Compaction time
- Compaction pressure
- Roll face and surface condition

Johanson [32] devised a compaction pressure diagram showing the optimum pressure and also showing the importance of the cheek rolls. The cheek rolls are where it covers the powder material between the main land areas and maximizes the

### C. Roll Design, Roll Surface

Compactor rolls rotate in the same speed. Usually, one has a frame. The other shaft has a pressure is applied on both halves. Compaction pressure is delivered (Fig. 2). For additional information on compaction, see Dehont et al. [33]. A mathematical model calculation of the angle between the rolls. This work shows the angle and the internal friction. In effect very compressible material whereas incompressible material

Johanson [34] describes a smooth surface. The rough roll gripping region with granules that the deeper the roll position compaction. In summary the of the material flow properties pressure [34]. Note: The material relation pertaining to the

nip angle varies according to the material, to some degree, to the nature of the characteristics of the rolls [30]. Adjusted for intended needs.

olved over the years. By the mid-1970s, roll design improvements that improved conditions were identified, at that time, and minimized the leakage of un-

enter the gripping zone. The material enters into the narrowest part of the roller gap, distributed as uniformly as possible across the powder mass.

Researchers worked on improving feeding methods to satisfy and maximize the foregoing conditions identified were [31] the following:

Surface, rather than a flat roller pair

and flaps  
—cylindrical, or tapered-shaped  
variable feed screw controllers  
double screw feed systems

strength of a bulk solid material

- Particle size
- Particle density
- Type of binders
- Material moisture

ure for each solid material that, if

exceeded, will produce a lower-strength compact. The decrease in compact strength is caused by the excessive pressure degrading the individual particles. Factors influencing roll briquetting press designs were identified by Johanson [32]:

- |                                   |                              |
|-----------------------------------|------------------------------|
| • Material flow properties        | • Roll diameter              |
| • Material variability properties | • Roll gap range             |
| • Material compressibility        | • Pocket depth               |
| • Compaction time                 | • Feed pressure torque range |
| • Compaction pressure             | • Feed screw location        |
| • Roll face and surface           | • Cheek plate design         |

Johanson [32] devised mathematical equations to predict maximum press pressure and also showed the most effective way to achieve the maximum pressure by increasing the roll diameter size. Particularly, he noted the importance of the cheek plate design. The cheek plate protrudes into the roll gap where it covers the side land areas. This in effect, confines the powder material between the rolls and reduces the pressure build-up in the side land areas and maximizes the force pressure evenly across the rolls.

### C. Roll Design, Roll Surface, and Nip Angle

Compactor rolls rotate in the reverse direction to one another at exactly the same speed. Usually, one horizontal shaft is not movable in the compactor frame. The other shaft has some horizontal play or movement. Hydraulic pressure is applied on both housings of the movable roll. By this means, the compaction pressure is delivered to the rolls and subsequently to the material (Fig. 2). For additional information pertaining to the functional theory of compaction, see Dehont et al. [33]. Johanson [34] developed a thorough mathematical model calculating the nip angle and the pressure distribution between the rolls. This work concluded that two key factors, surface friction angle and the internal friction angle (friction of material) affect the nip angle size. In effect very compressible materials have large nip angles ( $\sim 30^\circ$ ), whereas incompressible materials have small nip angles ( $\sim 7-10^\circ$ ).

Johanson [34] described the advantages of a rough roll surface versus a smooth surface. The rough rolls can drag the compacting material into the roll gripping region with greater force than smooth rolls. He also indicated that the deeper the roll pockets, the smaller the pressure ratio applied at compaction. In summary the pressure exerted by the compactor is a function of the material flow properties, roll size, roll gap, roll surface, and the feed pressure [34]. Note: The mathematical model did not include vacuum deaeration relation pertaining to the nip angle.

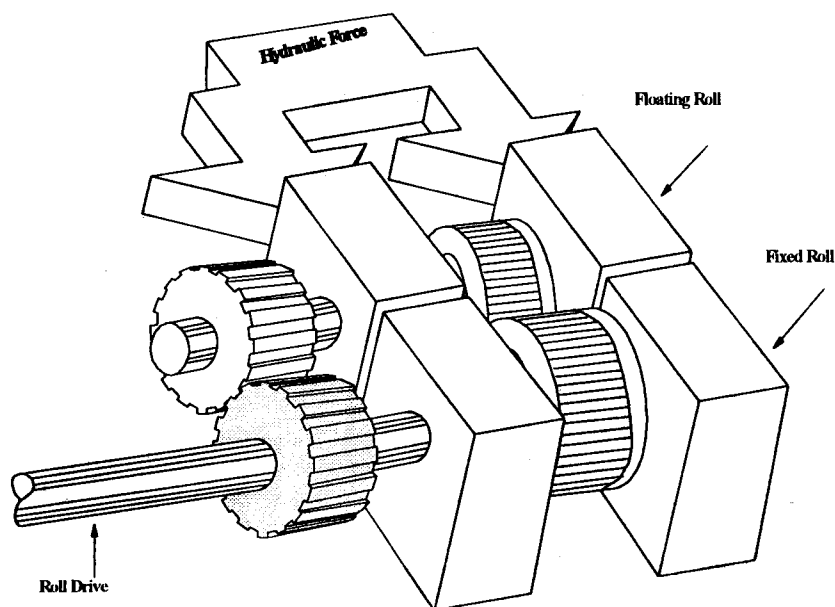


Fig. 2 Typical design rolls; one floating role and one fixed roll.

Johanson [35] described and illustrated three regions which material passes through during roller compaction: (a) slip region, (b) nip angle region, and (c) release region. These regions are characterized by their position related to the rolls, forces, and timing of the material passing through each zone. The slip region occurs before the nip region and is where particles begin slipping at the roll surfaces and where some plastic deformation of solid occurs. As time increases, the roll surfaces create a downward motion on the powder through roll frictional forces. The effectiveness of the slip region is related to the friction between the rolls and the material and the internal friction of the material. Powder compressibility, bulk density, and solids contact pressure occur in the nip angle region. The release region happens immediately after the compact formation. Generally, the size of the release region is dependent on the powder's elastic properties.

#### D. Roll Design Features

Because of powder feed unevenness in the nip and roll gap regions, unavoidable powder leak is produced during the compaction process. This situation produces excessive unwanted fines and undesirable raw material.

Usually, this problem is caused by the powder feed unevenness. Under these conditions are normally avoided by feeding the powder into tablets or capsules.

Trials performed by F. J. Parrott [12] showed that chutes fitted at the end of a roller compaction material feed across the roller ends minimized the effects of having concavoconvex rolls (a feature counteracted side seal effect on the edges). They also designed a roller compaction that allowed the powder feed to be controlled width. This design minimized the side seal effect.

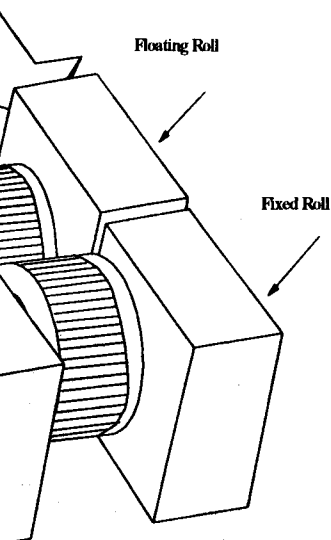
Funakoshi et al. [30] showed that powder is not delivered adequately to the pressing zones. This occurs due to the powder flow. Their work showed that the compaction pressure (used to compact across the roller ends because of the side seal effect) newly designed concavoconvex rolls minimized the adverse side seal fracture. The selection of rimmed rollers was shown to be a solution zone and also conveyed the material. Parrott concluded that the height of the roller end exceeded the side seal effect. A side seal effect was leakage during the compaction process. At the rim, the fines leakage was minimized by the rim and pressure distribution across the rimmed-shaped rolls. It was shown that the side seal was still dependent on the powder properties.

Parrott [12] further studied the side seal wall design. He demonstrated that the side seal with the rollers when under pressure. The shape of the inner wall design was shown to be compressed. This design minimized the side seal effects.

#### E. Feed System Issues

The objective of roll compaction is to produce a sufficient strength that it meets the compaction and lometry specifications. The





and one fixed roll.

ed three regions which material slip region, (b) nip angle region, characterized by their position the material passing through each nip region and is where particles are some plastic deformation of faces create a downward motion es. The effectiveness of the slip e rolls and the material and the compressibility, bulk density, and angle region. The release region nation. Generally, the size of the s elastic properties.

e nip and roll gap regions, un- g the compaction process. This s and undesirable raw material.

Usually, this problem is caused by an uneven compact formed when the powder is fed toward the middle of the roll width. Granules produced under these conditions are normally not optimal for further pharmaceutical processing into tablets or capsules.

Trials performed by Funakoshi et al. [30] with rectangular aperture chutes fitted at the end of a feed screw, partially aided in preventing uneven material feed across the roll width. They also demonstrated the positive effects of having concavoconvex roller pair fitted with inner ring walls. This feature counteracted side seal effects (fractured or incomplete compact edges). They also designed and tested other rolls (concavoconvex with rim) that allowed the powder feed to distribute more uniformly across the roll width. This design minimized powder leakage during compaction.

Funakoshi et al. [30] showed that when the roll rim inner angle is zero, powder is not delivered adequately and evenly to the gripping and compressing zones. This occurs because the stationary side seals act as resistors to the powder flow. Their work demonstrated that the formed compact and the compaction pressure (using standard rolls) produced an uneven compact across the roller ends because of side seal friction. When they employed the newly designed concavoconvex-rimmed rolls, it protected the compact from the adverse side seal fracturing effect. They also determined [30] a proper selection of rimmed rollers that delivered adequate powder to the compression zone and also conveyed powder fully across the roller gap region. They concluded that the height and slope of the inner wall rims optimally influenced the side seal effect. A  $65^\circ$  inner wall slope produced 2.5–3.0% fines leakage during the compaction of lactose. When the roll had no inner wall rim, the fines leakage was 15%. In summary, they optimized the compact and pressure distribution along the roll by using the concavoconvex-rimmed-shaped rolls. It was also acknowledged that the best roll design is still dependent on the powder raw material properties [30].

Parrott [12] further substantiated the usefulness of the  $65^\circ$  angle inner wall design. He demonstrated that a greater area of powder is in contact with the rollers when under this condition. The height of the rim and the shape of the inner wall determines the amount of powder that is gripped and compressed. This design minimized side wall seal frictional fracture effects.

## E. Feed System Issues

The objective of roll compaction is to consistently make an agglomerate of sufficient strength that it meets the required powder density and granulometry specifications. The key-operating goal of the compactor is to main-

tain a range of pressure on the feed stock independent of the fluctuating material size fed to the rolls.

Historically, the compaction process was managed by controlling the infeed, the quantity per unit of time, the roll speed, and the roll gap. Allowing the roll gap to float unchecked influences the production rate and the compact quality. Therefore, it is important to control the compaction process by setting a constant powder feed rate during the compaction operation.

Design innovations on the powder feed side of the roller compaction process are interesting and complex. The complexity is double-edged: powder materials that flow and move well are more easily handled on the feed side of the compactor. These types of materials generally do not necessarily need significant densification to improve their flow-handling characteristics on a large scale.

On the other hand, poor-flowing and low-density powders require special equipment and considerations to feed a compactor. Additionally, it is necessary to maintain a constant powder flow and quantity of material to the rolls during the compaction process. Therefore, the delivery feed system plays a very important role in delivering poor-flowing, low-density bulk powder materials to the roll compactor.

### 1. *Force-Feeding Screws*

The total compaction power requirement is the sum of the power required for the feed screws and the roll drive. Feed screws not only convey the powder material from the compactor storage hopper, but they also help deaerate the powder in the process. The deaeration of the powder acts as a minicompactor by precompressing the material just before roll compaction. Optimum compaction pressures and feed screw designs vary widely with powder material properties. Changes in bulk powder density and feed screw speeds will affect the roll gap, the compaction pressure, the throughput, and the quality of the compact.

Weggle [36] indicates that feed screw torque varies directly with the precompaction pressure. He suggests that by maintaining a constant feed screw pressure, the compactor operator can control the compact quality. Variations in precompaction pressure and in the compacting pressures are directly related to feed screw amperages and the roll drive motor. Of course, the compaction pressures are dependent on a continuous flow of powder material into the feed screw area. If the powder feed flow is intermittent or interrupted, this will affect the feed screw amperage readings and eventually the roll drive readings. Weggle [36] notes that force feeding of material deaerates the feed material and reduces the roll pressure loads. Generally, it is more efficient to achieve total densification during several stages of the roller compaction process.

## 2. *Feed Screw Designs*

The design of vertical cylinders is not uniform around the circumference. The rotation does not coincide with the feed direction. The drawback is that the powder is not fed uniformly to the rolls; the middle of the rolls receives more powder. This situation creates a poor compact weak at the ends that may give rise to uncompacted material. A more uniform design, provides a more uniform compact and area than a single feed system.

## F. Deaeration Theory

A key factor limiting compaction is air entrapment in materials. The air between powder particles are forced through the powder flow causing a nonuniform compact density.

Johanson [37] predicted that air entrapment effects could be handled by critical-compacting pressure, ammeter, powder permeability, and applying these principles in compacting that a compactor operator would not exceed maximum pressures to increase in-feed flow rates.

### 1. *New Machine Design:*

The evenness of the powder compact is a function of compaction. Most roller-compaction is a function of powder leakage; namely, the formulation and equipment design. The powder feed and powder slippage on the roll surfaces. Because of this effect, the compacted powder. This is a function of Under these conditions, an increased cycle time occurs.

is independent of the fluctuating

was managed by controlling the roll speed, and the roll gap. Allowances the production rate and the ability to control the compaction process during the compaction operation.

Free side of the roller compaction complexity is double-edged: powder is more easily handled on the feed side. Materials generally do not necessarily have their flow-handling characteristics

Low-density powders require special handling in a compactor. Additionally, it is difficult to control the flow and quantity of material to the rolls. Therefore, the delivery feed system for poor-flowing, low-density bulk

is the sum of the power required to drive the feed screws not only convey the material through the hopper, but they also help with the deaeration of the powder acts as a precompaction just before roll compaction. Feed screw designs vary widely with material bulk powder density and feed screw rotation pressure, the throughput, and

Power torque varies directly with the roll speed by maintaining a constant feed rate. One can control the compact quality. Variations in the compacting pressures are controlled by the roll drive motor. Of course, on a continuous flow of powder, the powder feed flow is intermittent or fluctuates in temperature readings and eventually leads to force feeding of material into the rolls, increasing roll pressure loads. Generally, it is difficult to maintain uniform conditions during several stages of the

## 2. Feed Screw Designs

The design of vertical cylindrical feed screws tend to feed powder solids uniformly around the circumference of the feed screw. This physical situation does not coincide with the general rectangular compactor throat design. The drawback is that the powder infeed is not delivered evenly across the rolls; the middle of the rolls have more powder fed to it than the edges. This situation creates a poor-quality compact; a strong middle compact, and a compact weak at the ends because of frayed edges. Frayed compact edges give rise to uncompacted material and excess fines. A multiple feed screw design, provides a more uniform powder distribution across the rolls in depth and area than a single feed screw does in either vertical or horizontal positions.

## F. Deaeration Theory

A key factor limiting compaction production throughput and compact quality is air entrapment in materials. During compression air-occupying voids between powder particles are compressed and squeezed. The gas pushes through the powder flow causing powder fluidization and a nonuniform level of powder at the roll gap. These situations limit throughput and create a nonuniform compact density.

Johanson [37] predicted theoretical compactor-operating conditions to handle air entrapment effects in materials. In general, he concluded that the critical-compacting pressure level is dependent on the roll speed, roll diameter, powder permeability, compressibility, and compact strength. When applying these principles in commercial application, Johanson [37] indicated that a compactor operator would have to operate the press at slightly less than maximum pressures to allow for material inconsistencies and variable in-feed flow rates.

### 1. New Machine Design: Vacuum Deaeration

The evenness of the powder feed into the rolls largely determines the success of compaction. Most roller-compacting systems suffer from the disadvantage of powder leakage; namely, 20–30% of powder particles (depending on the formulation and equipment design) are not compacted owing to uneven powder feed and powder slippage between individual loose particles and the roll surfaces. Because of this effect, it is usually necessary to recycle the uncompacted powder. This is a significant design and operational drawback. Under these conditions, additional equipment and costs are required, and increased cycle time occurs.

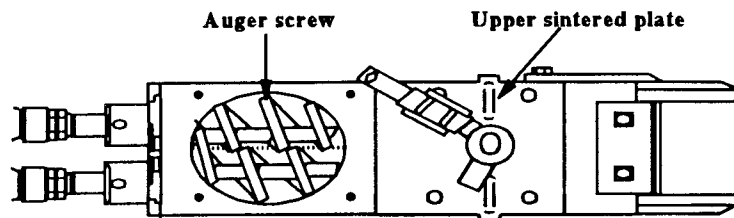
The roller compactor designs discussed so far suffer from two disadvantages: When bulk feed powder densities are less than  $0.3 \text{ g/cm}^3$ , the compaction throughput efficiency decreases and, concurrently, the uncompacted powder leakage generally increases.

A recent new machine improvement in powder compaction has not been extensively discussed in the literature. Essentially it involves vacuum deaerating the powder material just before roller compaction. The multiple benefits of such action have been significant and remarkable results have been observed when compacting low-density raw materials [31]:

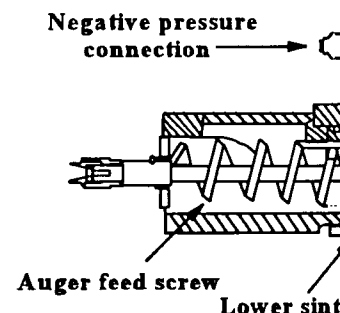
- More uniform powder feed to the rollers
- Less voltage and amperage variability for the roll pair
- More uniform and strong compact
- Less powder leakage
- Higher yield
- Less powder adhering to the compact before sizing
- Higher compact throughput per time
- Fewer airborne particles

The newly designed equipment involves a compactor, fitted with two horizontal feed screws, that features vacuum deaeration [31]. Specifically, the roll compactor is equipped with a conical storage hopper containing a variable speed agitator. Bulk powder is fed directly from the top of the hopper to the top of twin horizontal auger feed screws that transport the powder to the nip roll area (Fig. 3).

A novel encasing that leads to the compactor rolls encloses the variable-speed auger screws. Just before the nip area, a pair of sintered stainless steel plate segments are assembled within the horizontal auger feed system, which can operate under partial vacuum (Fig. 4). A small, self-contained vacuum pump draws negative pressure through a dry filter and a stainless steel line to the sintered assembly. The partial vacuum is adjustable from  $-0.1$  to  $-0.8$  bar.



**Fig. 3** Top view of auger feed screws and powder transport mechanism with upper sintered plate.



**Fig. 4** Side view of auger feed system.

The compaction rolls are mounted on heavy-duty bearings in support frames. The upper roll is slightly movable to adjust the nip pressure. Deaeration, auger feed, and roll pressure are the main factors in producing a compact (Fig. 5). The compact is then reeled off for processing requirements.

## 2. Vacuum Deaeration Technology

To evaluate the effectiveness of the vacuum deaeration system, a low-density material was designed to process a large quantity of material. The activated deaeration system was used to compacted with the deaeration system. The material was not compacted when it was not compacted.

During multiple trials, the material (low density) were processed with the vacuum deaeration system. The compacted material was not compacted at a specific screw speed. The compacted material was not compacted at a 10-mesh screen to determine

sed so far suffer from two disadvantages are less than  $0.3 \text{ g/cm}^3$ , the and, concurrently, the uncompacted.

at in powder compaction has not e. Essentially it involves vacuum e roller compaction. The multiple cant and remarkable results have sity raw materials [31]:

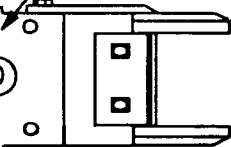
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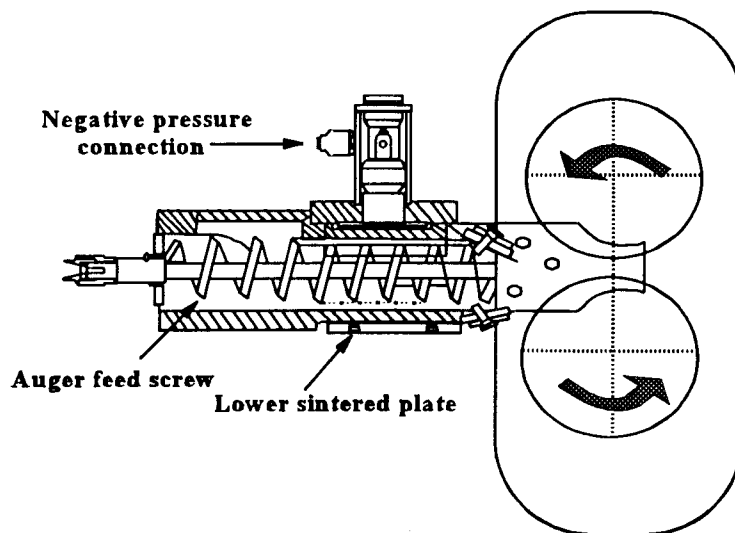


Fig. 4 Side view of auger feed screw system and sintered plate segment.

The compaction rolls can operate at different speeds and are supported on heavy-duty bearings in such a way that the lower roll is fixed and the upper roll is slightly movable in the vertical plane. The deaerated material passes through the roll pair, which is under infinitely variable hydraulic pressure. Deaeration, auger feed speed, roll speed, and hydraulic pressure are the main factors in producing a compact with specified properties (Fig. 5). The compact is then reduced by rotary granulators to meet future-processing requirements.

## 2. Vacuum Deaeration Trials and Results

To evaluate the effectiveness of the compactor's deaeration system, a test was designed to process a low-density active drug blend with and without the activated deaeration system. The test showed how much material was compacted with the deaeration system engaged and how much material was compacted when it was not engaged. The test also determined how much material was not compacted (powder roll leakage) in each case [31].

During multiple trials, weighed powder blends ( $0.25\text{--}0.35 \text{ g/cm}^3$  density) were processed with the deaeration system engaged. The material was compacted at a specific screw feed rate, roll speed, and roll pressure. The compacted material was not sized. Instead, it was carefully collected on a 10-mesh screen to determine the compact and leakage quantities. In the first

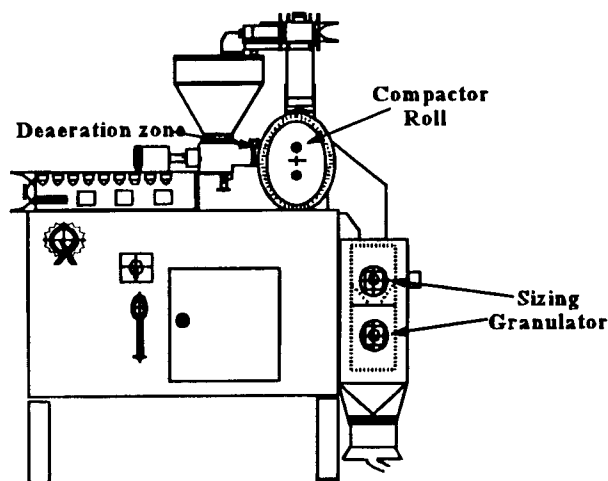


Fig. 5 Compactor side view illustrating powder deaeration zone.

experiment, when under the influence of vacuum deaeration, the compactor produced throughputs of 100 kg/h and the resultant noncompacted material leakage rate was less than 2%. Because the vacuum deaeration was very effective and resulted in only limited leakage of noncompacted material, there was no need to recirculate the noncompacted powder back to the rolls to meet processing specifications.

Under a second set of compacting conditions, vacuum deaeration was not activated and the process typically produced 70–80 kg/h of densified compact. The powder leakage rate increased to 20–30%. During this set of conditions, the powder flow to the roll pair was uneven and the ribbon compact was not uniform. Processing this formulation for a long period under these conditions would require recirculation equipment to return the uncompacted powder to the rolls. The compactor parameters are described in Table 2 (trials 1 and 2) [38].

A second experiment was conducted with a different formulation involving the same active drug substance and the same active quantity per unit dose. This experiment replicated the design of the first experiment. The powder feed was processed and compacted with and without the deaeration system. The rates of compaction were measured in the same manner as the first experiment. The compaction parameters were purposefully optimized at a roll speed of 8 rpm. When the deaeration system was activated, the compactor yielded 150 kg/h and the powder leakage rate was only 0.9%. When

**Table 2** Compactor Operating Conditions for Flowing, Low-Density Active Drug Substances with and without Deaeration and Nonvacuum Deaeration

#### Conditions

##### Formulation 1

Powder density (g/cm <sup>3</sup> )
Screw feed (rpm)
Roll speed (rpm)
Vacuum (bars)
Roll pressure (bars)
Compact rate (kg/h)
Compact leakage rate (kg/h)

##### Formulation 2

Powder density (g/cm <sup>3</sup> )
Screw feed (rpm)
Roll speed (rpm)
Vacuum (bars)
Roll pressure (bars)
Compact rate (kg/h)
Compact leakage rate (kg/h)

the vacuum deaeration was not activated, the compactor produced 100–110 kg/h with a powder leakage rate of 20–30% [trials 1 and 2] for parameter set 1.

Both experiments clearly demonstrated that vacuum deaerating the bulk powder before compaction provided increased throughput (compared to compaction without vacuum deaeration) compared to compaction without vacuum deaeration.

Several compactor manufacturers have developed vacuum deaeration systems. The purpose of this study was to compare how two different compactor designs would perform when compacting a low-density formulation. The design of the first machine is shown in Fig. 5 and the design of the second machine is shown in Fig. 6.

To evaluate the effectiveness of the vacuum deaeration system, a test similar to the one described in the previous section (compaction trials with and without vacuum deaeration) was carried out. The objective was to measure the powder density of the feed stock from

**Table 2** Compactor Operating Conditions and Throughput Yields for Poor-Flowing, Low-Density Active Drug Blend, Formulations 1 and 2. Vacuum Deaeration and Nonvacuum Deaeration Trials

Conditions	Trial 1	Trial 2
<b>Formulation 1</b>		
Powder density (g/cm <sup>3</sup> )	0.25–0.35	0.25–0.35
Screw feed (rpm)	52	52
Roll speed (rpm)	8	8
Vacuum (bars)	–(0.78–0.80)	0
Roll pressure (bars)	60–65	60–65
Compact rate (kg/h)	100	70–80
Compact leakage rate (kg/h)	2	15–20
<b>Formulation 2</b>		
Powder density (g/cm <sup>3</sup> )	0.25–0.35	0.25–0.35
Screw feed (rpm)	52	52
Roll speed (rpm)	8	8
Vacuum (bars)	–(0.78–0.80)	0
Roll pressure (bars)	60–65	60–65
Compact rate (kg/h)	150	100–110
Compact leakage rate (kg/h)	1.3	20–30

vacuum deaeration, the compactor resultant noncompacted material in the vacuum deaeration was very large of noncompacted material, compacted powder back to the rolls

In addition, vacuum deaeration was produced 70–80 kg/h of densified material to 20–30%. During this set of trials, the air was uneven and the ribbon compaction formulation for a long period of time. The compaction equipment to return the compactor parameters are described

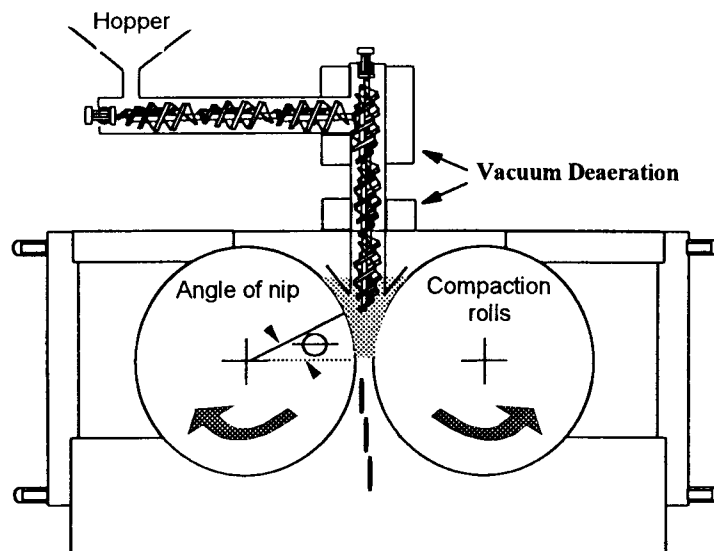
With a different formulation in addition to the same active quantity per sign of the first experiment. The compaction with and without the deaeration was measured in the same manner as the compaction system were purposefully optimized at the compaction system was activated, the compaction rate was only 0.9%. When

the vacuum deaeration was not activated, the compaction process typically produced 100–110 kg/h with 20–30% powder leakage [38] (see Table 2 [trials 1 and 2] for parameter settings and results).

Both experiments clearly demonstrated the importance of vacuum deaerating the bulk powder before compaction. In addition, the second formulation provided increased compaction throughput (with or without the vacuum deaeration) compared with the first formulation.

Several compactor machine companies are developing and perfecting vacuum deaeration systems. A comparative test was designed to determine how two different compactor machine designs, with vacuum deaeration, perform when compacting a low-bulk-density active drug substance. The design of the second machine's feed system and vacuum deaeration is shown in Fig. 6.

To evaluate the effectiveness of each compactor's vacuum deaeration system, a test similar to the ones conducted and described earlier in this section (compaction trials employing and not employing vacuum deaeration) was carried out. The objective of these trials was to increase the active bulk density of the feed stock from 0.22 g/cm<sup>3</sup> to 0.61 g/cm<sup>3</sup>.



**Fig. 6** Compactor force-feeding system illustrating horizontal and vertical combination force feed auger screws with deaeration: compactor design 2.

Compactor, machine 1, containing the horizontal twin screws and the vacuum deaeration design as described in Fig. 4, produced granules with 0.63–0.64 g/cm<sup>3</sup> density at 80 kg/h yield. When the vacuum deaeration was not activated the desired granule density could not be achieved (see Table 3A [trials 1 and 2] for operating parameters and results of compactor machine design 1).

The second compactor's vacuum deaeration system, machine 2 (see Fig. 5), proved to be adequate in densifying the active drug granules during the first vacuum deaeration trial. Even after a second compaction pass with vacuum deaeration (trial 2) the powder density was increased only to 0.58 g/cm<sup>3</sup>. It was apparent that the level of vacuum being applied to the active drug substance in machine 2 was insufficient or ineffective, even at a maximum machine vacuum deaeration level [38] (see Table 3B [trials 1, 2, and 3] for machine 2 operating parameters and results).

During the trials, it was noted that the vertical cylindrical feed screw on machine 2 (see Fig. 6) had a tendency to cake-up between the feed screw flutes. The vertical cylindrical screw appeared clogged. This situation could have diminished the positive effects of machine 2's vacuum deaeration. It appears that machine 2's vacuum deaeration pressure could not penetrate

**Table 3** Operating Parameters  
2 When Compacting Poor-Flow

Conditions

A. Design 1

Initial density (g/cm <sup>3</sup> )
Powder density (g/cm <sup>3</sup> )
Screw feed (rpm)
Roll speed (rpm)
Vacuum (bars)
Roll pressure (bars)
Compact rate (kg/h)

B. Design 2

Initial density (g/cm <sup>3</sup> )
Powder density (g/cm <sup>3</sup> )
Screw feed (horizontal; rpm)
Screw feed (vertical; rpm)
Roll speed (rpm)
Vacuum (bars)
Roll pressure (bars)
Compact rate (kg/h)

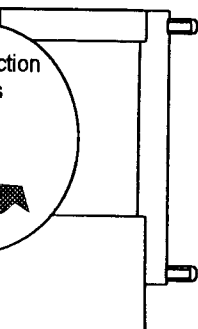
the clogged powder contained in the feed screw flutes to deaerate the material effectively.

In conclusion, the experimental results show that screw feed speed, roll speed, compaction rate, and the compaction pressure are the most important parameters in the first compactor's deaeration system. The vacuum deaeration feed powder unit design and process eliminated powder leakage and powder degradation equipment. The first compactor (see Fig. 4) proved to be superior to the second compactor (see Fig. 6) in compacting an active bulk drug with a high degree of compaction. A new critical condition, vacuum deaeration, was being roller-compacting effect.

There are now four key parameters that can minimize uncompacted powder



vacuum Deaeration



operating horizontal and vertical com-  
 : compactor design 2.

horizontal twin screws and the  
 Fig. 4, produced granules with  
 When the vacuum deaeration was  
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vertical cylindrical feed screw  
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 n pressure could not penetrate

**Table 3** Operating Parameters and Results of Compactor Machine Designs 1 and 2 When Compacting Poor-Flowing, Low-Density Active Drug Substance

Conditions	Trial 1	Trial 2	
A. Design 1			
Initial density (g/cm <sup>3</sup> )	0.22	0.22	
Powder density (g/cm <sup>3</sup> )	0.63–64	0.45	
Screw feed (rpm)	52	52	
Roll speed (rpm)	8	8	
Vacuum (bars)	0.65	0	
Roll pressure (bars)	50	50	
Compact rate (kg/h)	80	42	
	Trial 1	Trial 2	Trial 3
B. Design 2			
Initial density (g/cm <sup>3</sup> )	0.22	0.45	0.22
Powder density (g/cm <sup>3</sup> )	0.45	0.58	0.46
Screw feed (horizontal; rpms)	30	30	30
Screw feed (vertical; rpms)	260	260	260
Roll speed (rpm)	6	6	6
Vacuum (bars)	0.34	0.34	0
Roll pressure (bars)	50	50	50
Compact rate (kg/h)	40	48	36

the clogged powder contained in the vertical fluted screw sufficiently enough to deaerate the material effectively [38].

In conclusion, the experiments evaluated the effects of powder density, screw feed speed, roll speed, roll pressure, vacuum deaeration pressure, compaction rate, and the compaction leakage rate. Test results demonstrated that the first compactor's deaeration and feed system designs significantly increases compaction output. This was achieved by concentrating the vacuum deaeration feed powder uniformly across the compaction rolls. This new equipment design and process provided high compact yields and virtually eliminated powder leakage, obviating the need for expensive powder recirculation equipment. The first compactor's vacuum deaeration design (see Fig. 4) proved to be superior to the second (see Fig. 6) when compacting an active bulk drug with a density of approximately 0.2 g/cm<sup>3</sup>. In summary, a new critical condition, vacuum deaeration, has been identified in optimizing roller-compacting effectiveness and efficiency [38].

There are now four key conditions that optimize roller compaction and minimize uncompacted powder leakage:

1. Adequate powder supply must enter the gripping zone.
2. Powder must be fully conveyed into the narrowest part of the roller gap.
3. Compaction pressure must be distributed as uniformly as possible over the whole of the roller-gripped powder mass.
4. Vacuum deaeration must be effectively distributed before the nip roll region.

## V. EQUIPMENT SUPPORT SYSTEMS

Roller compaction is a continuous process, but compaction technology, specifically the activities before and after compacting, contains additional processing steps. It requires processing equipment to control and transport the bulk powder to the compactor. The technology also requires processing equipment to size and transport the treated granules into storage containers for future processing.

Different raw material powders behave in different ways and can require unique equipment to support feed stock movement to a compactor. This can be a troublesome and tiring task. Attention is required by engineering, manufacturing, and technology personnel to understand what the critical processing steps are, along with the equipment and product requirements. Specific feeding equipment must be selected or designed to provide a certain amount of bulk powder to the compactor in a timely manner to meet operational needs. The prevention of flow problems into the compactor is as important as compactor design innovations. It is clear from previous writings and discussions that the powder feed must be available in sufficient supply for effective and efficient quality roller compaction. Insight into sound-engineering concepts and practices interfacing bulk powder movement, by gravity or preferably pneumatic conveyance with storage bin systems, are crucial in the compaction technology process.

The requirement of reliable feed stock movement and storage is based on sound equipment and engineering designs so that powder discharge is on-demand in a predictable and reliable manner. Important points need to be addressed from engineering and technological perspectives to ensure that optimum material-handling systems are in place to support compacting granulation technology. Selective equipment support system issues and questions are raised in this section for the reader:

1. Identify batch process system requirements:
  - Evaluate and identify solids handling and feeding requirements, including health, safety, and environmental issues.

- Determine time
  - Select and design
  - Identify current
2. Identify and evaluate process.
    - What are the steps receiving raw material, to after-product?
    - What are the steps to be changed?
    - Raw material in behavior?
    - How much space?
    - Bulk powder compaction process control, inventory space, cost?
    - Which raw material fed sequentially?
    - Can the bulk powder be moved to process or after?
  3. Determine the time
    - What are the time materials before?
    - What is the next step?
    - Are the dry in suited to the process?
    - Can small-quantity one-for-one process?
    - Evaluate process time, transport, what constraints gain?
    - What is the bulk influence powder systems can be powder efficiency?
  4. Bulk powder-feeding
    - Analyze handling
    - Analyze time cost

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- Determine time available for solids handling and feeding steps.
  - Select and design handling and feeding equipment based on compactor throughput needs.
  - Identify current and future processing needs.
2. Identify and evaluate each handling step throughout the entire process.
    - What are the step-by-step physical movements of the powder: receiving raw materials, to stock storage, to process room storage, to after-process storage requirements?
    - What are the storage constraints, and how can the constraints be changed?
    - Raw material ingredients: what type, quantity, and handling behavior?
    - How much space is available for bulk powder storage?
    - Bulk powder container or package: can it be changed to optimize process conditions? (minimize container handling and inventory space, documentation, and logistics).
    - Which raw materials can be combined, or do they have to be fed sequentially?
    - Can the bulk powder be transported continuously without having to be moved mechanically in segment quantities during the process or after processing?
  3. Determine the time for solids handling and feeding steps:
    - What are the time and distance constraints to move the raw materials before and after compacting-sizing?
    - What is the next processing step and what are the purposes of the step?
    - Are the dry ingredients received in packages or containers suited to the process usage rate now or in the future?
    - Can small-quantity ingredients be received in containers on a one-for-one process batch basis?
    - Evaluate process storage time, feed process time, containerizing time, transport time: What is the rate determining time step, what constraints can be changed for what cost and time gain?
    - What is the bulk powder flow rate? Does vibration or air influence powder movement? What mechanical or air transflow systems can be employed before compaction to move the bulk powder efficiently?
  4. Bulk powder-feeding systems: what are the considerations?
    - Analyze handling and feeding methods.
    - Analyze time constraints.

- Analyze cost constraints.
  - Analyze other requirements: environment and ergonomics.
5. The ideal equipment support system provides the following:
    - It automatically transfers all ingredients at the correct feed rate.
    - It is easy to clean.
    - The process equipment train is simple, efficient, and cost-effective.
    - The flow of materials requires transport systems that are efficient in design and operator useable, and provides fast delivery of materials to a strategic location ready for the next processing step.
    - The equipment support system meets current good manufacturing practices, and complies with current environmental health and safety regulations.
  6. Equipment needs and designs have to consider the following aspects for an effective and efficient process:
    - Ingredients' physical characteristics.
    - Required feed rate.
    - Amount of each ingredient.
    - Cross-contamination constraints.
    - Container holding each ingredient.
    - Equipment ergonomic requirements.
    - Health and safety regulations.
  7. What bulk conveying equipment is appropriate to use?
    - Vacuum pneumatic conveyor; removes powder from a container and transfers it to a filter receiver that separates the powder from the airstream and discharges it into a hopper.
    - Dense-phase pneumatic conveyor: uses air pressure to transfer slugs of powder from a pressure vessel to a storage vessel. The powder is emptied from a container into the pressure vessel. When the vessel is full, its inlet is sealed, and the vessel is then pressurized. The vessel's discharge valve is opened and ingredients are pushed as powder slugs into the conveying line into a storage container.
    - Dilute-phase pneumatic air pressure: the powder is emptied from a surge hopper and then flows through a rotary valve feeder into the conveying line, where it is suspended in a continuously flowing airstream. The rotary valve provides a continuous seal between the pressurized container and the atmospheric storage container.
    - Other more common conveyors are disk, screw, bucket, and belt.

8. Container discharge
  - What are the design considerations (e.g., segregation), the system for the bins?
  - The concept of acceptable manufacturing to personnel, containers, and transport

## VI. CLEANING AND CLEANING GUIDELINES

Equipment cleaning and cleaning guidelines focus on equipment use. It is impossible to present any one guideline without prefacing it with a disclaimer: cleaning programs will vary from product to product and is dependent on the products being cleaned. There is never only one correct method for cleaning. The pharmaceutical industry has developed guidelines for equipment cleaning.

- 21 CFR, Part 211.6
- FDA Guideline to Industry, July, 1993

As described earlier in this chapter, a process equipment train. It includes the compactor. These equipment requirements are for shape, and performance for equipment requirements are for the company. Even within multi-product manufacturing processes, there is no equipment similarity. Each product has its own volume requirements, and economic requirements for a compactor support system. In the end, the design and selection of equipment impinge on the nature and type of equipment.

Currently, there are no guidelines for the equipment train—raw materials and storage vessels—can be cleaned.

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#### 8. Container discharge:

- What are the discharge patterns, the flow properties (is there segregation), the container geometry, discharge rate, and feeder system for the following containers: bags, cartons, drums, and bins?
- The concept of delivering bulk powder is critical in obtaining acceptable manufacturing efficiencies. Considerations pertaining to personnel, handling equipment, feeding methods, containers, and transport systems are interrelated.

## VI. CLEANING AND CLEANING VALIDATION GUIDELINES

Equipment cleaning and cleaning validation go hand in hand. This discussion focuses on equipment used in nonsterile oral solid-dosage forms. It is impossible to present any one view or scheme for compactor-cleaning validation without prefacing it with the comment that equipment-cleaning validation programs will vary from company to company. Cleaning validation is dependent on the products manufactured and the equipment design. There is never only one correct method, procedure, or way to accomplish the cleaning goal. The pharmaceutical industry is directed by two legal directives for equipment cleaning:

- 21 CFR, Part 211.67, Vol. 58.147/August, 1993
- FDA Guideline to Inspections of Validation of Cleaning Processes. July, 1993

As described earlier in the text, roller compaction technology involves a process equipment train. It consists of pieces of equipment before and after the compactor. These equipment pieces are very specific and vary in design, shape, and performance for each manufacturers' needs. The compaction equipment requirements are very rarely duplicated, within the plant or the company. Even within multinational pharmaceutical companies, who have similar manufacturing processes at other international sites, there is usually no equipment similarity. Each plant's physical considerations, product volume requirements, and economics are the key drivers for each plant's compactor support system. In the long run, these are the key factors that influence the design and selection of the hardware and, therefore, directly impinge on the nature and type of equipment cleaning required.

Currently, there are no compactor clean-in-place (CIP) systems. Parts of the equipment train—raw material containers and process-receiving storage vessels—can be cleaned by CIP methods. Other pieces of equipment,

such as compactors, mills, vacuum transport devices, and logistical transport sections, require manual cleaning.

### A. Compactor Materials and Construction

Compactors are made from hardened steel and stainless steel and food-grade plastic polymers. These product contact surfaces and exterior noncontact surfaces should be designed in such a manner to facilitate cleaning: smooth surfaces and no ledges. Equipment parts that need to be disassembled should be designed to be taken apart quickly and efficiently and easily cleaned. Compactor roll construction should be designed in cantilevered style. This type of construction expedites roll disassembly and aids in cleaning contact parts. The roll pair should be manually movable, or rotatable when the machine is in the cleaning mode. Contact gaskets should be designed with each of washing and drying in mind. Auxiliary vacuum pumps need to be accessible for routine filter cleaning and equipment maintenance. Transport support systems also need to be designed for quick and efficient disassembly, cleaning, and assembly.

### B. Cleaning Approaches

Typical cleaning-validation approaches vary from examining the most difficult product to clean (the most adhering, the most potent, or the most toxic) to determining how effective the equipment cleaning procedures are. Examining the equipment process train or individual pieces of equipment is an important factor. However, there are also other objectives: the safety of the cleaning process, the environmental effect, and the ease of validation. How clean is clean enough? This is a question that must be answered on a case-by-case basis.

### C. Cleaning Concepts and Elements

With this focus in mind, a cleaning validation program needs to be certain about: Why? How? When? Limits? Relation to reality?

The essentials of a good cleaning validation program will contain the following elements:

- Scope
- Objectives
- Procedures
- Acceptance criteria
- Responsibilities

The written cleaning program should include:

1. Detailed written cleaning procedures
2. Equipment cleaning procedures
3. Cleaning validation procedures
4. Cleaning validation procedures
5. Change control procedures
6. Approval system

### D. Tests

After the equipment is cleaned, how do we know the equipment cleanliness?

- Perform a visual inspection
- Sample the cleaned equipment for residue, identity, UV-visible spectroscopy, and microbiology with clean water.
- Swab test the most difficult areas for residue. Perform analytical tests as justified.

Visual equipment inspection is a good starting point, but water, and swab testing the equipment are more definitive methods in the pharmaceutical industry. There are efficient methods to measure the cleanliness of equipment and to validate them by the US Food and Drug Administration. These methods require sensitive and specific detection. Each method has its own limitations. Samples have to be taken at random and can give false results owing to contamination. To compensate for each disadvantage, a combination makes good technical sense.

### E. Limits

Several pharmaceutical companies have established the US Environmental Health Agency (EPA) levels. Subject exposure limits are set. An acceptable residue limit is calculated based on the amount of the residual product in the subsequent product, and is used to determine the day. The *acceptable residual*

t devices, and logistical transport

## uction

and stainless steel and food-grade surfaces and exterior noncontact surfaces to facilitate cleaning: smooth surfaces that need to be disassembled should be designed efficiently and easily cleaned. Surfaces designed in cantilevered style. This design helps in cleaning contact surfaces that are movable, or rotatable when the equipment is disassembled. Gaskets should be designed with easy access for cleaning. Auxiliary vacuum pumps need to be designed for equipment maintenance. Transport equipment should be designed for quick and efficient disassembly,

y from examining the most difficult cleaning procedures are. Examining individual pieces of equipment is an important objective: the safety of the equipment and the ease of validation. How much time must be answered on a case-

ion program needs to be certain that the program is in reality? A validation program will contain the

The written cleaning procedures should contain

1. Detailed written cleaning procedures
2. Equipment cleaning log
3. Cleaning validation protocol
4. Cleaning validation record
5. Change control mechanism
6. Approval system

## D. Tests

After the equipment is cleaned, which test method does one use to determine equipment cleanliness?

- Perform a visual equipment inspection.
- Sample the cleaned equipment rinse water and perform conductivity, UV-visible spectral scans, and pH tests, and compare the results with clean water.
- Swab test the most difficult equipment access areas and perform analytical tests as just mentioned.

Visual equipment inspection, sampling the cleaned equipment rinse water, and swab testing the cleaned equipment are widely used sampling methods in the pharmaceutical industry. The latter two are effective and efficient methods to measure and assure qualitatively and quantitatively cleanliness of equipment and have been publicly supported and approved by the US Food and Drug Administration (FDA). However, both methods require sensitive and specific analytical techniques for drug and detergent detection. Each method has technical weaknesses: swabbing, because samples have to be taken at random locations, and rinse water, because samples can give false results owing to the active drug substance's poor solubility. To compensate for each disadvantage, an approach combining both methods makes good technical sense.

## E. Limits

Several pharmaceutical companies follow the cleaning limit standards set by the US Environmental Health Affairs Department for nonobservable effect levels. Subject exposure limit (sel) are set by drug and safety experts. The acceptable residue limit is calculated by a validation method. The sel is the amount of the residual product or solvent allowed in a daily dose of the subsequent product, and is usually expressed in milligrams per subject per day. The *acceptable residual limit* is the concentration of product or solvent

obtained in rinse water or swabs that will provide a quantity no greater than the sel residual.

## VII. SCALE-UP

There is no such thing as a standard approach to solve compactor scale-up or equipment changes in the pharmaceutical production process. It is also true that considerations, approaches, and examples presented have been experienced by others and are not all-inclusive. This chapter section does offer specific compaction scale-up and equipment process changeover concepts experienced by the author and associates. No single written article could hope to provide universal guidance. On the other hand, the best way to solve these types of challenges is to attack them systematically. This usually can be achieved through appropriate qualifications and validation efforts; at times, through trial and error approaches before start-up; through knowing equipment and processing capabilities and limitations; and through an understanding of raw material variabilities.

Discussion about solid-dosage form scale-up, specifically in this section, does not infer compliance with suggested scale-up and postapproval change (SUPAC) guidelines. The described work does not necessarily provide recommendations to meet tests and filing requirements for changes in manufacturing processes and equipment. Scale-up guidance for immediate-release solid-dosage forms and postapproval changes have been published [39]. Readers are encouraged to familiarize themselves through the reference noted.

Elements of scaling-up a pharmaceutical compaction process or equipment change involve several issues and technologies. There are numerous considerations that go beyond the specific process technology transfers that evolve from the pilot plant to the manufacturing technical operations center. Most of these concerns are centered around the plant's current operations, and its previous use or manufacture of dry granulations using roller compaction technology.

The scope of the scale-up involves the following issues not directly related to the compaction process technology transfer: Is the scale-up in a first world country or in a third world country? What type of equipment manufacturer support is expected in either country? What is the reputation or reliability of the equipment manufacturer in the United States or in the country where the start-up will occur? What is the equipment manufacturer's customer service record worldwide? How many days will it take to replace a broken or worn part? Does the equipment manufacturer carry a reliable stock parts inventory? What is the pharmaceutical corporation's commitment

to technology and engineering will provide the training: the or the international engineer the in-process-testing equipment on site, qualified, and operated in a non-English-speaking technical operations site be in communications and learning? What (equipment and process)? The concerns that go beyond the hardware before the project start-up. Do receiving site key personnel, development, engineering and technology scale-up permit a transition and transfer.

Additional concepts to be scale-up project team do their accurate? Does everyone know with the overall project? Has materials? Has the quality lab ing? Are the technical experts support—vendor and technology systems, and process questions

- What?
- Where?
- Why?

A brief scale-up evaluation

1. Experience: What is
  - First-time technology
  - Training requirements process training technology department
2. Logistic matters: Do
  - Throughput control of the warehouse stock
  - Number of drums
  - Distance between
  - Strategic location movement, and



provide a quantity no greater than

ach to solve compactor scale-up  
cal production process. It is also  
examples presented have been ex-  
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he following issues not directly  
gy transfer: Is the scale-up in a  
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country? What is the reputation  
er in the United States or in the  
is the equipment manufacturer's  
many days will it take to replace  
nt manufacturer carry a reliable  
utical corporation's commitment

to technology and engineering support before and after the start-up? Who will provide the training: the equipment manufacturer, the operations staff, or the international engineering—pharmaceutical technology staffs? Will the in-process—testing equipment and necessary analytical equipment be on site, qualified, and operational when needed? If the scale-up is completed in a non—English-speaking country, will someone from the receiving technical operations site be involved in the start-up to facilitate communications and learning? Who will perform the validation requirements (equipment and process)? These are some of the key questions and concerns that go beyond the hardware issues and that need to be addressed before the project start-up. Discussing and planning these issues with the receiving site key personnel, equipment manufacturers, research and development, engineering and technology members, well in advance of the technology scale-up permit a smoother more successful process technology transition and transfer.

Additional concepts to be concerned with during the scale-up: Did the scale-up project team do their homework? Are communications timely and accurate? Does everyone know where the team now is, and where it is going, with the overall project? Has the quality control laboratory approved all raw materials? Has the quality laboratory completed product qualification testing? Are the technical experts prepared and available to provide the timely support—vendor and technology? Have the following equipment, support systems, and process questions been asked and answered?

- |          |         |
|----------|---------|
| • What?  | • When? |
| • Where? | • How?  |
| • Why?   | • Who?  |

A brief scale-up evaluation checklist follows:

1. Experience: What is the plant's technology background?
  - First-time technology versus in-house technology.
  - Training requirements: who will provide the equipment and process training—equipment manufacturer or in-house technology department?
2. Logistic matters: Did the room design and location take advantage of the warehouse storage location or manufacturing?
  - Throughput considerations
  - Number of drum or bulk transfers
  - Distance between operational steps
  - Strategic locations: speed of communications, speed of bulk movement, and next-step considerations

3. Engineering support requirements: Does the manufacturing room design meet manufacturing operational requirements?
  - Water
  - Air
  - Lighting
  - Floor space
  - Cleaning
  - cGMPs
4. Raw material delivery system: What tests were evaluated?
  - Feed system design testing and qualifying
  - Powder flow and containment evaluation
  - Timing—individual operations versus the whole operation
  - Logistics—first-floor manufacturing versus two-floor processing
5. Compactor machine design: What are the plant's compacting needs?
  - Compactor performance: product quality and volume issues versus costs
  - Small to large compactor: same vendor, but different models
  - Small to large compactor: different vendor and different models
  - Compactor design: deaeration versus nondeaeration capabilities
6. Environmental issues: Does the manufacturing room and equipment comply with standards?
  - Airborne particles: dust controls and exposure limits
  - Noise abatement: limits
  - Lighting: can operators read and write in the room
7. Raw materials: What is the raw material variability?
  - First-time use versus used in previous formulations (first-time chemical development scale-up, or is it a raw material characteristic change).
  - Safety issues: handling hazards or others

### A. Scale-Up Case Studies

The compaction scale-up examples that follow illustrate evaluation methodologies for equipment design, process evaluation, and equipment differences.

#### 1. Vacuum Deaeration Equipment Design Evaluation

Pilot compaction trials were conducted to investigate the vacuum deaeration effect when compacting an antibiotic powder with 0.2 g/mL density. The study determined the compact throughput, compact density, and fines not

**Table 4** Compactor Parameters

Trial (no.)	Vacuum deaeration (15 Hg)	Roll pressure (kN)
1	No	50
2	No	50
3	Yes	105
4	Yes	50
5	Yes	70

compacted during vacuum deaeration. The parameters of the compaction process were

- Vacuum deaeration
- Roll pressure
- Roll speed
- Screw speed
- Room temperature

The equipment feed deaerated directly above the rolls, and the deaeration capability. A high-compression hopper, fed the powder directly into the rolls. Trials were conducted with and without deaeration. The fines were fully collected directly on a roll. The fines were compacted (those particles that were not compacted) and were weighed and separated from the compact. The results are noted in Table 4.

The conclusions drawn from the trials, with this equipment design, were that the fines (noncompacted powder) were not compacted. The roller, unpublished compactor to

#### 2. Wet Granulation Technology, versus Roller Compaction

A highly water-soluble drug was used to make capsules. The active drug sub-

**Table 4** Compactor Parameter Settings and Compact Physical Properties

Trial (no.)	Vacuum deaeration (15 Hg)	Roll pressure (kN)	Roll speed (rpms)	Screw speed (rpms)	Compact density (g/mL)	Compact rate (g/min)	Fines not compacted (%)
1	No	50	4.8	27	1.05	604	7.1
2	No	50	6.8	98	1.07	1172	8.1
3	Yes	105	4.8	27	1.21	772	5.6
4	Yes	50	6.7	27	1.11	848	5.8
5	Yes	70	5.2	27	1.25	856	5.8

compacted during vacuum deaeration when employing a new equipment feed design. The parameters that were controlled and monitored during the compaction process were

- Vacuum deaeration
- Roll pressure
- Roll speed
- Screw speed
- Room temperature and humidity

The equipment feed design consisted of a funnel storage hopper, located directly above the rolls, which was retrofitted with vacuum deaeration capability. A high-compression feed screw, fitted inside the funnel storage hopper, fed the powder directly into knurled rolls. The compaction trials were conducted with and without vacuum deaeration. The compact was carefully collected directly on a 10-mesh screen. Particles that were not compacted (those particles that were not attached to the compact), for example, fines by-passing roll compaction and the nonadhering compacted particles, were weighed and separated. The compact was not sized. The parameters are noted in Table 4.

The conclusions drawn from this trial indicated that vacuum deaeration, with this equipment design, increased the compaction rate, reduced the fines (noncompacted powder), and increased the compact density [RW Miller, unpublished compactor technical notes, June 1996].

## 2. *Wet Granulation Technology, versus Slugging Technology, versus Roller Compaction Technology*

A highly water-soluble drug was to be incorporated at 35% into hard gelatin capsules. The active drug substance characteristics were as follows:

- Small needle-shaped particles
- Low bulk density,  $\approx 0.1$  g/mL
- Extremely poor flow
- "Sticky"
- Highly compressible

Initially, a conventional wet granulation process was investigated. This process was not feasible owing to the extreme high solubility of the active bulk drug. When granulating, pockets of highly wetted area formed, preventing uniform moisture distribution and granule formation. Additionally, granulating with a solution of the drug was not acceptable because the amorphous form of the compound was formed after drying.

Given the encountered difficulties during the wet granulation process, the formulation scientist developed a dry-slugging granulation process. This process had some deficiencies. For example, it was difficult to compress the slugs to a similar consistency because of the extremely low bulk density and poor blend flow properties. Additionally, the weight and hardness of the slugs varied throughout the slugging powder process, and from batch to batch. This situation created a final blend (batch to batch) nonconsistency in particle size distribution, bulk, and tap densities (Table 5A). Additionally, owing to the extremely poor flowing powder blend, the process was not amenable to table scale-up. The slugging time took 10 h to process 100 kg of blend.

By using the same active drug blend, 2- to 5-kg pilot compaction trials were conducted. The compactor was fitted with deaeration capability. Results from numerous trials indicated batch-to-batch consistency in particle size distribution, bulk, and tap densities (see Table 5B). The compaction process was scaled-up to a rate of 100–150 kg/h using the same parameters as in the pilot trials. The granules manufactured from the compactor scale-up produced superior tablet physical properties compared with the slugging process [F Nikfar, unpublished technical notes, May 1996].

### 3. Slugging versus Compaction Technology

A new antibiotic tablet was introduced internationally in three countries. Two countries did not have compactors to manufacture the product. Their process consisted of the following:

- |                            |                        |
|----------------------------|------------------------|
| • Blend ingredients        | • Slug blend           |
| • Mill blend               | • Size slugs           |
| • Blend milled ingredients | • Compress sized slugs |

In the third country, roller compaction was substituted for the slugging process. Although the sizing of the slugs and compacts was completed on

**Table 5A** The Physical Properties of the Slugging Process

Lot no.	Mesh		
	30	50	80
N93C018C <sup>a</sup>	18.3	38.0	15.0
N93J071C <sup>a</sup>	15.8	30.0	17.0
N93M109C <sup>a</sup>	16.3	33.5	19.0
N94D053 <sup>a</sup>	19.8	36.1	19.0
N94G101C <sup>a</sup>	8.9	40.9	19.0
N94H117C <sup>a</sup>	8.6	26.5	22.0
N95006 <sup>a</sup>	11.7	31.2	19.0
N95008 <sup>a</sup>	15.4	33.8	20.0
N95044 <sup>a</sup>	13.6	35.5	22.0
N95134 <sup>a</sup>	7.8	27.5	22.0

<sup>a</sup>Sized by oscillator equipped with 20 mesh.

**Table 5B** The Physical Properties of the Compactor Process

Lot no.	Screw <sup>a</sup> speed (rpm)	Roll pressure bar	Mesh	
			30	50
I	45	62.5	19.4	3.0
II	38	62.5	18.8	4.0
III	38	50.0	14.2	4.0
IV	38	75.0	15.1	4.0
V	30	62.5	11.6	3.0
VI	53	62.5	12.6	4.0
VII	38	62.5	16.4	4.0

<sup>a</sup>The roll speed and vacuum deaeration were controlled. The roller compactor was equipped with a vacuum deaeration ducted using an oscillator equipped with 20 mesh.

different machines, and the results were consistent. In each situation, the tablets' physical properties and content uniformity relative standard deviation were routinely achieved. The process was completed higher within 30 min in each

**Table 5A** The Physical Properties of the Final Blends Manufactured Using the Slugging Process

Lot no.	Mesh size (% retained)							Bulk density	Tap density
	30	50	80	100	120	200	Pan		
N93C018C <sup>a</sup>	18.3	38.0	15.5	6.6	5.5	9.3	6.8	0.58	0.71
N93J071C <sup>a</sup>	15.8	30.0	17.1	7.1	6.2	10.9	12.8	0.56	0.72
N93M109C <sup>a</sup>	16.3	33.5	19.7	7.4	6.9	10.4	5.8	0.47	0.68
N94D053 <sup>a</sup>	19.8	36.1	19.2	5.6	4.7	7.6	6.9	0.52	0.75
N94G101C <sup>a</sup>	8.9	40.9	19.7	6.2	4.4	8.9	11.0	0.60	0.87
N94H117C <sup>a</sup>	8.6	26.5	22.9	9.7	6.7	10.8	14.7	0.49	0.78
N95006 <sup>a</sup>	11.7	31.2	19.9	8.4	5.8	8.7	14.3	0.58	0.81
N95008 <sup>a</sup>	15.4	33.8	20.2	7.0	6.0	8.3	9.3	0.58	0.80
N95044 <sup>a</sup>	13.6	35.5	22.4	8.9	5.7	8.8	5.1	0.51	0.73
N95134 <sup>a</sup>	7.8	27.5	22.9	7.7	7.6	10.8	15.8	0.57	0.76

<sup>a</sup>Sized by oscillator equipped with 20-mesh screen.**Table 5B** The Physical Properties of the Blends Manufactured Using the Roller Compactor Process

Lot no.	Screw <sup>a</sup> speed (rpm)	Roll pressure bar	Mesh size (% retained)							Bulk density	Tap density
			30	50	80	100	120	200	Pan		
I	45	62.5	19.4	39.9	14.0	5.7	3.8	5.7	11.4	0.60	0.69
II	38	62.5	18.8	43.2	12.9	5.2	3.3	3.9	12.6	0.60	0.72
III	38	50.0	14.2	41.2	16.2	6.3	3.9	3.4	14.8	0.60	0.72
IV	38	75.0	15.1	42.2	16.1	5.8	3.5	3.8	13.5	0.60	0.70
V	30	62.5	11.6	37.7	16.2	6.8	4.2	1.7	21.8	0.60	0.72
VI	53	62.5	12.6	40.6	17.4	7.0	4.4	1.5	16.5	0.58	0.70
VII	38	62.5	16.4	40.7	15.2	5.4	3.6	1.6	17.2	0.58	0.71

<sup>a</sup>The roll speed and vacuum deaeration were kept constant at 8 rpm and -0.2 atm, respectively. The roller compactor was equipped with a 5-mm primary screen. The final sizing was conducted using an oscillator equipped with 20-mesh screen.

different machines, and the particle size results were not exactly the same in each situation, the tablets' content uniformity results were equivalent. The content uniformity relative standard deviations of 1.5–2.0% ( $n = 10$  tablets) were routinely achieved. The tablet dissolution profiles averaged 95% or higher within 30 min in each country.

**Table 6A** The Granulometry of Powder Blends  
Manufactured Using Slugging Technology in Country A

Lot no.	Mesh size (% retained accumulated)					Pan
	80	100	140	300	325	
I	59	64	71	78	84	100
II	51	57	65	73	82	100
III	57	62	69	74	79	100

Slugging parameters: 4 tons tooling pressure, 0.75-in. flat-faced tooling, slug weight, 0.8–1.0 g; slug hardness, 12–18 Strong Cobb units, sized through oscillator, 16-mesh screen.

**Table 6B** The Granulometry of Powder Blends  
Manufactured Using Slugging Technology in Country B

Lot no.	Mesh size (% retained accumulated)					Pan
	20	40	60	100	200	
I	9	28	42	60	67	100
II	9	27	41	59	66	100
III	9	27	41	58	65	100

Slugging parameters: 4-tons tooling pressure; 0.75-in. flat-faced tooling; slug weight, 0.8–1.0 g; slug hardness, 12–18 Strong Cobb units; sized through oscillator, 1.1-mm screen.

**Table 6C** The Granulometry of Powder Blends  
Manufactured Using Compaction Technology in Country C

Lot no.	Mesh size (% retained accumulated)					Pan
	20	40	60	100	200	
I	23	51	63	73	80	100

Compactor parameters: roll pressure, 62–65 bars; roll speed, 8 rpms; horizontal feed screw, 52 rpms; deaeration, –0.2 bars; sized by double rotary granulators prebreaker, 4 mm; sizing screen, 1.2 mm.

The success to process t of 250–900 kg) and achieve r due to the robustness of the f pressibility characteristics. Ill served and equipment param are noted in Tables 6A–C [RV 1996].

## VIII. COMPACTOR VALIDATION

### A. Compactor Process Validation

Roller compactor process validation is briefly discussed in this section. Validation guidance and issues are discussed in [40–43].

*Process validation* is defined as a high degree of assurance that a final product meeting its preestablished quality attributes. Three aspects that define process validation are consistency, and predetermining what is to be validated, it requires full understanding of requirements), combined with data. Both collection and interpretation of data, especially, how the data are collected, are more important than the data itself.

The conditions, manner, and timing of data ultimately determine their utility for process control and total quality management. The tools and procedures that are used to find and evaluate the cause-and-effect relationships in a controlled process variabilities are developed through controlled experiments, either at the laboratory or the scientific method in action. The goal is to know well a process performs. Process validation efforts and written procedures are essential.

### B. Equipment Qualification

MM Tuckerman [Process equipment qualification]. Temple University Pharmacy School identifies a pharmaceutical process

ends n Country A		
ccumulated)		
	325	Pan
	84	100
	82	100
	79	100

5-in. flat-faced tool-  
Strong Cobb units,

ends n Country B		
ccumulated)		
	200	Pan
	67	100
	66	100
	65	100

5-in. flat-faced tool-  
Strong Cobb units;

ends in Country C		
umulated)		
	200	Pan
	80	100

oll speed, 8 rpms;  
s; sized by double  
1.2 mm.

The success to process the tablet formulation (with varying batch sizes of 250–900 kg) and achieve reproducible tablet physical results were partly due to the robustness of the formulation design and the active drug's compressibility characteristics. Illustration of the different granulometries observed and equipment parameters employed to achieve the desired results are noted in Tables 6A–C [RW Miller, unpublished technical notes, January 1996].

## VIII. COMPACTOR VALIDATION AND QUALIFICATION

### A. Compactor Process Validation

Roller compactor process validation and equipment qualification subjects are briefly discussed in this section. Pharmaceutical solid-dosage process validation guidance and issues are well addressed in the following references [40–43].

*Process validation* is described as documented evidence that provides a high degree of assurance that a specific process will consistently produce a final product meeting its predetermined specifications and quality attributes. Three aspects that define process validation are documented evidence, consistency, and predetermined specifications. For a manufacturing process to be validated, it requires full-scale batch manufacturing (achieving the requirements), combined with scientific judgment based on good scientific data. Both collection and interpretation of data are vitally important. Particularly, how the data are collected is as important or even more important than the data itself.

The conditions, manner, and procedures used to find and collect the data ultimately determine their value. Torbeck [44] notes that statistical quality control and total quality management are passive in data collection. They are tools and procedures that only observe what is happening. They do not find and evaluate the cause-and-effect relations to understand, answer, and control process variabilities or unknowns. Torbek [44] suggest that controlled experiments, either at the laboratory or on the production floor, are the scientific method in action, proving or disproving the measure of how well a process performs. Personnel involved with roller compaction process validation efforts and written protocols should be wise to these precepts.

### B. Equipment Qualification

MM Tuckerman [Process equipment validation: unpublished technical notes, Temple University Pharmacy School, September 1986] noted, that one *validates* a pharmaceutical process and *qualifies* a piece of equipment. Com-

compactor equipment qualification begins a long time before the machine is installed in the plant. Elements of good equipment qualification begin with equipment specifications, installation qualification, operation and performance qualification, and operator-training qualification.

Equipment specifications of the compactor powder delivery system and the compactor require written protocols that specify the user's needs. Specification requirements should include the following

- Functional purpose of compactor and system
- Materials of construction
- Operating environment
- Installation location
- Capacity and speed
- Delivery system design
- Equipment integration
- Product usage
- Product stability
- Raw material characteristics
- End product characteristics
- Cleaning requirements
- Specification references

The specifications also need to elaborate about the environmental and facility needs

- Safety codes
- Equipment noise and airborne particle restrictions
- Floor space and weight restrictions
- Instrumentation, calibration, and control requirements
- Maintenance documentation

Installation qualification and calibration ensures that the powder delivery system and the compactor performance aspects are properly defined and checked. Services for the material delivery system and the compactor room, such as electricity, water, compressed air, and lighting are verified that they meet electrical and mechanical codes.

Operational and performance qualification provide assurances that the equipment is capable of doing what it is intended to do. Before the performance testing, it is advisable that a testing protocol be jointly authored by plant engineering, pharmaceutical technology, manufacturing, and validation personnel. This shared written protocol provides different views for the qualification and lots of equipment ownership.

Operational qualification parameters include basic equipment functions determined by technical measurements:

- Roll speed
- Vacuum pressure
- Feed screw speed
- Hydraulic oil and water pressures
- Sizing equipment speed
- Powder delivery speed

Compactor operational qualification also includes operator and maintenance training in the following areas:

- Safety and emergency
- Operational hands-on
- Operational and maintenance
- Parts replacement procedure
- Basic equipment troubleshooting

Generally, the better the qualification, the better the product.

## IX. FUTURE TRENDS AND CHALLENGES

Pharmaceutical roller compaction has advanced through engineering and innovation to the industry and the customer. At least one recent survey, that of the current granulation technology [3].

The lack of use and innovation in roller compaction technology by innovator and generic manufacturers is a process technology. At the moment, these attitudes and preferences are not changing. A published study pertaining to the lack of use or preferences. It appears that the lack of use is why certain process technologies are not used. Compactor equipment fabrication is necessary to change and to improve. Manufacturers' technology preferences would be useful in determining the future of the process and evolve during the next decade in the pharmaceutical industry worldwide.

I believe there is a lack of investment (50,000 US dollars) for universities and companies may not see this as a viable option for expanding. However, if manufacturers change technology preferences, the technology available for use at the moment (technologists). Small laboratories can deliver 15–25 kg/h of compacted material. In plastics, where possible, to improve the deaeration of the powder blend, the equipment is appropriately fitted with monodisperse



long time before the machine is equipment qualification begin with qualification, operation and performance qualification.

compactor powder delivery system and that specify the user's needs. Specifications following

- Equipment integration
- Product usage
- Product stability
- Raw material characteristics
- End product characteristics
- Cleaning requirements
- Specification references

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include basic equipment functions

- Hydraulic oil and water pressures
- Sizing equipment speed
- Powder delivery speed

also includes operator and main-

- Safety and emergency procedures
- Operational hands-on procedures with certification program
- Operational and maintenance manual use procedures
- Parts replacement procedures and timing
- Basic equipment trouble-shooting

Generally, the better the equipment installation and the performance qualification, the better the process start-up and roller compactor operation.

## IX. FUTURE TRENDS AND NEEDS

Pharmaceutical roller compaction equipment design and technology will advance through engineering and science. Developments will be in response to the industry and the customer's needs and requirements. It is evident from at least one recent survey, that apparently roller compaction does not fulfill the current granulation technology needs of the US pharmaceutical industry [3].

The lack of use and interest of roller compaction granulation technology by innovator and generic companies suggests little preference for this process technology. At the moment, there is no clear understanding why these attitudes and preferences exist in the United States. Also, there is no published study pertaining to international compaction technology attitudes or preferences. It appears that equipment manufacturers need to determine why certain process technology preferences exist. It is also apparent that compactor equipment fabricators need to determine what specific actions are necessary to change and to improve the pharmaceutical industry and formulators' technology preferences for roller compaction. This information would be useful in determining how roller compaction technology can improve and evolve during the beginning of the 21st century in the pharmaceutical industry worldwide.

I believe there is a lack of small roller compactors modestly priced (50,000 US dollars) for university and industry uses. Equipment compactor companies may not see this market segment as important or potentially expanding. However, if manufacturers want to understand, influence, and change technology preferences, they need to have their machines and technology available for use at the grass-roots level (for young scientists and technologists). Small laboratory model machines should be designed to deliver 15–25 kg/h of compact. They should be constructed with high-density plastics, where possible, to reduce weight and costs, and feature vacuum deaeration of the powder blend before compaction. The machine should be appropriately fitted with monitoring instrumentation.

From an industrial pharmaceutical technology perspective, roller compaction technology will evolve and advance from equipment manufacturers and technologists who effectively understand the industry and its process needs.

## REFERENCES

1. AW Pradhan, AV Bhalariao. Roll compaction techniques. *East Pharm (India)* 28:35-36, Oct, 1985.
2. EL Parrot, *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., N.Y., Vol 2. 1990, pp. 203-204.
3. RF Shangraw, DA Demarest Jr. A survey of current industrial practices in the formulation and manufacture of tablets and capsules. *Pharm Technol* January: 32-44, 1993.
4. R Cohn, H Heilig, A Delorimier. Critical evaluation of the compactor. *J Pharm Sci* 55:328-331, 1996.
5. A Falzone, G Peck, G McCabe. Effects of changes in roller compaction parameters on granulations produced by compaction. *Drug Dev Ind Pharm* 18: 469-489, 1992.
6. E Jerome, A Delacourte, J Guyot, P Hervieu, F Dupont. Effects of compactor adjustments on powder properties. *Proceedings of the 8th Pharmaceutical Technology Conference*, March 1989.
7. F Duhont, P Hervieu, E Jerome, J Guyot, A Delacourte. Effects of compactor adjustments on powder properties. *Proceedings of the 5th Congress International de Technology*, Paris: Pharmaceutique 1989, pp. 369-379.
8. E Jerome, A Delacourte, P Leterme, J Guyot. The measurement of resulting forces on a roller compactor. *Drug Dev Ind Pharm* 17:1571-1591, 1991.
9. A Hakanen, E Laine. Acoustic characterization of a microcrystalline cellulose powder during and after its compression. *Drug Dev Ind Pharm* 21:1573-1582, 1995.
10. A Hakanen, E Laine, J Jalonen, K Linsaari, J Jokinen. Acoustic emission during powder compaction and its frequency spectral analysis. *Drug Dev Ind Pharm* 19:2539-2600, 1993.
11. JR Johanson. Predicting limiting roll speed for briquetting presses. *Proceedings of the 13th Biennial Conference of the Institute for Briquetting and Agglomeration*, 13:89-99, 1973.
12. EL Parrott. Densification of powders by concavo-convex roller compactor. *J Pharm Sci* 70:288-291, 1981.
13. PJ Sheskey, T Dabash. Evaluation of various polymers as dry binders in the preparation of immediate-release tablet formulation by roller compaction. *Pharm Technol* 19:98-112, 1995.
14. M Mollan, M Celik. Characterization of directly compressible maltodextrins manufactured by three different processes. *Drug Dev Ind Pharm* 19:2335-2358, 1993.
15. S Makowska, KA Khan. Tablets prepared by dry granulation.
16. Y Ibrahim. Comparative study of roller compaction and direct compression methods. *Pharm Technol* 15:298-301, 1991.
17. Y Ibrahim. Investigations into the effects of roller compaction during manufacturing. *Makowski* 1985.
18. Y Ibrahim. Comparative study of roller compaction and direct compression methods. *Pharm Technol* 15:298-301, 1991.
19. H Vromans, AH De Boer. Studies on tableting process. *Pharm Technol* 1985.
20. H Seager, I Burt, J Ryden. Comparison of granule structure between granule structure and direct compression product Part 1. *Int J Pharm Technol* 1991.
21. H Seager, P Rue, I Burt, J Ryden. Comparison of granule structure, process of manufacture and direct compression product Part III. *Int J Pharm Technol* 1991.
22. P Rue, H Seager, I Burt, J Ryden. Comparison of granule structure, process of manufacture and direct compression product Part III. *Int J Pharm Technol* 1991.
23. AA Chalmers, PH Elworthy. The effect of excipients and the method of compaction on the properties of a Matodex. *Pharm Technol* 1976.
- 23a. LC Li, GE Peck. The effect of excipients and the method of compaction on the properties of a Matodex. *Pharm Technol* 1976.
24. PJ Sheskey, T Cabelka, N. Preparation of controlled-release tablets containing HPMC polymers and hydroxypropylmethacrylate. *Pharm Technol* 1994.
25. S Malkowska, K Khan. Tablets prepared by dry granulation.
26. PJ Sheskey, T Capelka. Tablets containing HPMC polymers and hydroxypropylmethacrylate.
27. PJ Sheskey, T Cabelka, N. Preparation of controlled-release tablets containing HPMC polymers and hydroxypropylmethacrylate.
28. Y Kawashima, H Takeuchi. Preparation of a sustained-release formulation of a substituted hydroxypropylcellulose. *Pharm Technol* 1827-1831, 1993.

technology perspective, roller compaction from equipment manufacturers stand the industry and its process

compaction techniques. East Pharm (India)

ms, Marcel Dekker, Inc., N.Y., Vol 2.

vey of current industrial practices in the and capsules. Pharm Technol January:

al evaluation of the compactor. J Pharm

s of changes in roller compaction pa- compaction. Drug Dev Ind Pharm 18:

rvreu, F Dupont. Effects of compactor proceedings of the 8th Pharmaceutical

ot, A Delacourte. Effects of compactor proceedings of the 5th Congress Interna- tique 1989, pp. 369-379.

Guyot. The measurement of resulting Ind Pharm 17:1571-1591, 1991.

trization of a microcrystalline cellulose on. Drug Dev Ind Pharm 21:1573-

nsaari, J Jokinen. Acoustic emission frequency spectral analysis. Drug Dev Ind

eed for briquetting presses. Proceed- of the Institute for Briquetting and Ag-

y concavo-convex roller compactor. J

arious polymers as dry binders in the t formulation by roller compaction.

f directly compressible maltodextrins ses. Drug Dev Ind Pharm 19:2335-

15. S Makowska, KA Khan. Effect of re-compression on the properties of tablets prepared by dry granulation. *Drug Dev Ind Pharm* 9:331-347, 1983.
16. Y Ibrahim. Comparative microbial contamination levels in wet granulation and direct compression methods of tablet production. *Pharma Acta Helv* 66: 298-301, 1991.
17. Y Ibrahim. Investigations on the microbial contamination of folic acid tablets during manufacturing. MSc dissertation, Bellow University, Zaria, Nigeria, 1985.
18. Y Ibrahim. Comparative microbial contamination levels in wet granulation and direct compression methods of tablet production. *Pharm Acta Helv* 66: 298-301, 1991.
19. H Vromans, AH De Boer, GK Bolhuis, CF Leck, KD Kussendrager, H Bosch. Studies on tableting properties of lactose. *Pharm Weekblad Sci Ed* 7:186, 1985.
20. H Seager, I Burt, J Ryder, P Rhue, S Murray, N Beal, J Warrack. Relationship between granule structure, process of manufacture and the tableting of granulated product Part 1. *Int J Pharm Technol Prod Manuf* 1:36-44, 1979.
21. H Seager, P Rue, I Burt, J Ryder, J Warrack. The relationship between granule structure, process of manufacture and the tableting of a granulated product. Part III. *Int J Pharm Technol Prod Manuf* 2:41-50, 1981.
22. P Rue, H Seager, I Burt, J Ryder. The relationship between granule structure, process of manufacture and the tableting of a granulated product. Part II. *Int J Pharm Technol Prod Manuf* 1:2-6, 1980.
23. AA Chalmers, PH Elworthy. Oxytetracycline tablet formations: the influence of excipients and the method of granulation. *J Pharm Pharmacol* 28:234-238, 1976.
- 23a. LC Li, GE Peck. The effect of agglomeration methods on the micromeritic properties of a Matodextrin product M150. *Drug Dev Ind Pharm* 16:1491-1503, 1990.
24. PJ Sheskey, T Cabelka, R Robb, B Boyce. Use of roller compaction in preparation of controlled-release hydrophilic tablets containing methylcellulose and hydroxypropylmethylcellulose polymers. *Pharm Technol* 18:132-150, 1994.
25. S Malkowska, K Khan. Effect of recompression on the properties of tablets prepared by dry granulation. *Drug Dev Ind Pharm* 9:331-347, 1983.
26. PJ Sheskey, T Capelka. Reworkability of sustained-release tablet formulation containing HPMC polymers. *Pharm Technol* 16:60-74, 1992.
27. PJ Sheskey, T Cabelka, R Robb, B Boyce. User of roller compaction in preparation of controlled-release hydrophilic matrix tablets containing methylcellulose and hydroxypropyl methylcellulose polymers. *Pharm Technol* 18:132-150, 1994.
28. Y Kawashima, H Takeuchi, T Hino, T Niwa, T Lin, F Sekigawa. Preparation of a sustained-release matrix tablet of acetaminophen with pulverized low-substituted hydroxypropylcellulose via dry granulation. *Chem Pharm Bull* 41: 1827-1831, 1993.

29. AM Falzone, et al. Effects of changes in roller compactor parameters on granulations produced by compaction. *Drug Dev Ind Pharm* 18:469–489, 1992.
30. Funakoshi, et al. The use of a novel roller compactor with a concavo-convex roller pair to obtain uniform compacting pressure. *Drug Dev Ind Pharm* 3(6), 555–573 (1977).
31. RW Miller. Advances in pharmaceutical roller compactor feed system designs. *Pharm Technol* 18:154–162, 1994.
32. JR Johanson. Factors influencing the design of the roll-type briquetting presses. Proceedings of the 9th Biennial Briquetting Conference, Oct. 1965, pp. 17–25.
33. F Dehont, P Hervieu, E Jerome, A Delacourte, J Guyot. Briquetting and granulation by compaction new-granulator-compacto for the pharmaceutical industry. *Drug Pharm* 15:2245–2263, 1989.
34. JR Johanson. A rolling theory for granular solids. *J Appl Mechanics* Dec: 842–848, 1965.
35. JR Johanson. Feeding roll presses for stable roll operation. *Bulk Solids Handling* 4:417–422, 1984.
36. RW Weggles. The basics of force feed roll briquetting. *Manuf Eng Mar*:107–109.
37. JR Johanson, BD Cox. Fluid entrainment effects in roll press compaction. Proceedings of the 20th Biennial Conference of the Institute for Briquetting and Agglomeration, Oct. 1987, pp. 251–263.
38. RW Miller. Vacuum deaeration advances in pharmaceutical roller compaction technology. Proceedings of the 24th Biennial Conference of the Institute for Briquetting and Agglomeration Institute, Oct. 1995.
39. A Rudman, L Lesko, H Malinowski, et al. Immediate-release solid dosage forms scale-up and post approval changes, guidance for industry. *Pharm Tech* Mar:50–78, 1996.
40. B Loftus, R Nash, Eds. *Pharmaceutical Process Validation*, Technical Series of Textbooks, Marcel Dekker, Vol. 23, 1984.
41. Pre/post approval issues for development and validation, US FDA Guideline, January 1994.
42. HL Avallone. Validation of solid oral and topical dosage forms, *Pharmaceutical Engineering* Jan.–Feb. 1984, pp. 14–18.
43. KG Chapman. The PAR approach to process validation. *Pharm Technol* 8: Dec. 1984, pp. 22–36.
44. L Torbeck, R Branning. Designed experiments a vital role in validation. *Pharm Technol* 20:1996, pp. 108–114.

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## High Shear Mi

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- III. GRANULE GROWTH
- IV. GRANULATION CH
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in roller compactor parameters on  
Drug Dev Ind Pharm 18:469-489,

r compactor with a concavo-convex  
pressure. Drug Dev Ind Pharm 3(6),

iller compactor feed system designs.

esign of the roll-type briquetting  
Briquetting Conference, Oct. 1965,

urte, J Guyot. Briquetting and gran-  
mpactor for the pharmaceutical in-

lar solids. J Appl Mechanics Dec:

le roll operation. Bulk Solids Han-

briquetting. Manuf Eng Mar:107-

t effects in roll press compaction.  
nce of the Institute for Briquetting  
63.

n pharmaceutical roller compaction  
nial Conference of the Institute for  
Oct. 1995.

al. Immediate-release solid dosage  
guidance for industry. Pharm Tech

rocess Validation, Technical Series  
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and validation, US FDA Guideline,

topical dosage forms, Pharmaceu-  
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cess validation. Pharm Technol 8:

nts a vital role in validation. Pharm

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## High Shear Mixer Granulators

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## I. INTRODUCTION

High shear mixers have been widely used in the pharmaceutical industry since the 1970s for blending and granulation [1,2]. The mixers are originally designed for mixing of thermoplastics and have later been adopted and re-designed to meet the Good Manufacturing Practice (GMP) requirements in the pharmaceutical industry. The high shear mixers have been further developed as a one-pot unit, including the drying process, by use of vacuum assist and microwave [3] or air-stripping systems. The high shear mixers have been applied to wet granulation, melt granulation, and pelletization, and are set up with process control systems.

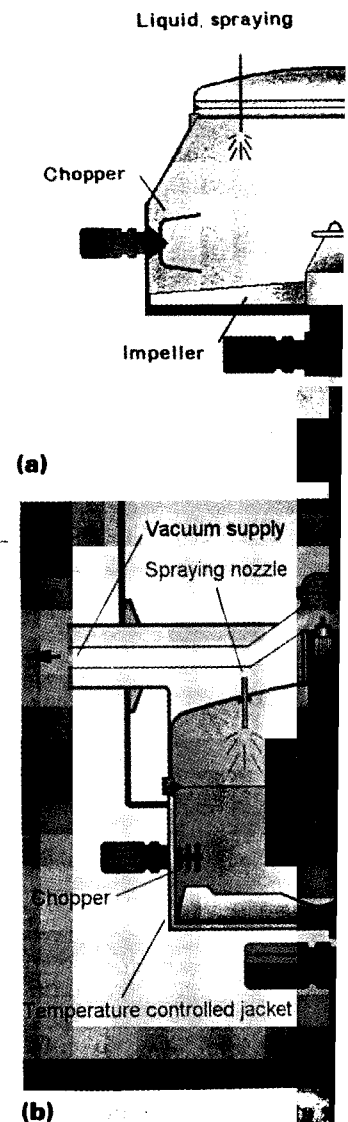
Blending and wet massing is accomplished by high mechanical agitation by an impeller and a chopper. Figure 1a shows a vertical high shear mixer, which is the most widely used version in the pharmaceutical industry. Mixing, densification, and agglomeration of wetted materials are achieved through shearing and compaction forces exerted by the impeller. The impeller rotates on a vertical shaft at a rotational speed corresponding to a radial blade tip speed of approximately 5–15 m/s. The chopper rotates at a similar tip speed which, because of its small diameter, corresponds to a very high rotation speed in revolutions per minute (rpm) (i.e., 1500–4000 rpm). The primary function of the chopper is to cut lumps into smaller fragments and aid the distribution of the liquid binder. The liquid binder is either poured into the bowl or sprayed onto the powder to achieve a more homogeneous liquid distribution. The granulation is conventionally performed in the following process steps:

1. Mixing of dry material at high impeller and chopper speeds for a few minutes (approx. 2–5 min)
2. Addition of liquid binder by pouring it onto the powder, while both the impeller and chopper are running at a low speed (approx. 1–2 min)
3. Wet massing with both agitators running at high speed (approx. 1–5 min)
4. Wet sieving the granules
5. Drying the granulate
6. Dry sieving the granulate

These steps are typical in production and may not be optimal for an individual product.

The advantages of granulation in high shear mixers are the following:

1. Short processing time.



**Fig. 1** (a) Schematic view PMA); (b) schematic view of shaft. Microwave and vacu (Aeromatic-Fielder, Spectrum)

d in the pharmaceutical industry on [1,2]. The mixers are originally have later been adopted and re- Practice (GMP) requirements in ear mixers have been further de- rying process, by use of vacuum systems. The high shear mixers elt granulation, and pelletization, s.

plished by high mechanical agi- re 1a shows a vertical high shear on in the pharmaceutical industry. of wetted materials are achieved exerted by the impeller. The im- tional speed corresponding to a 15 m/s. The chopper rotates at a ll diameter, corresponds to a very ute (rpm) (i.e., 1500–4000 rpm). cut lumps into smaller fragments nder. The liquid binder is either powder to achieve a more ho- tion is conventionally performed

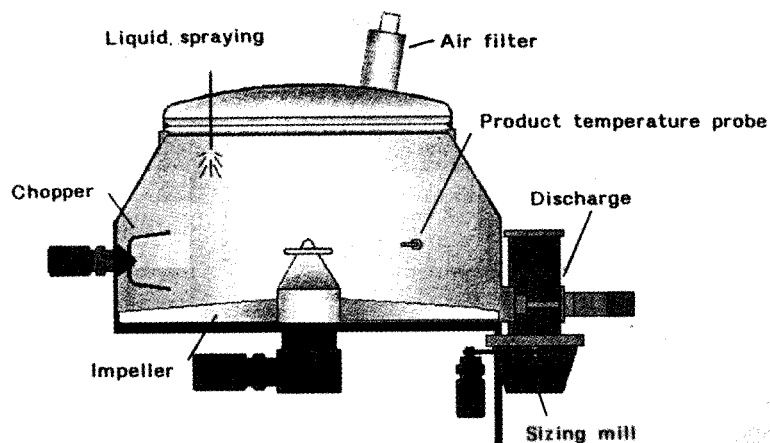
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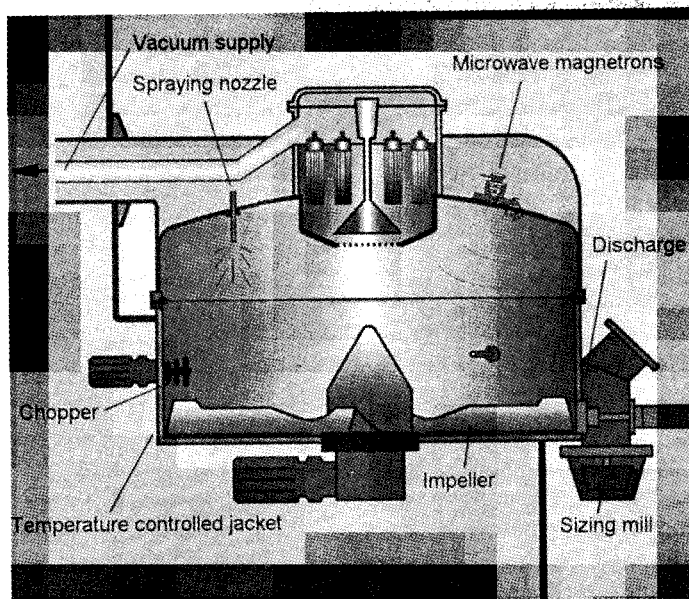
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n shear mixers are the following:

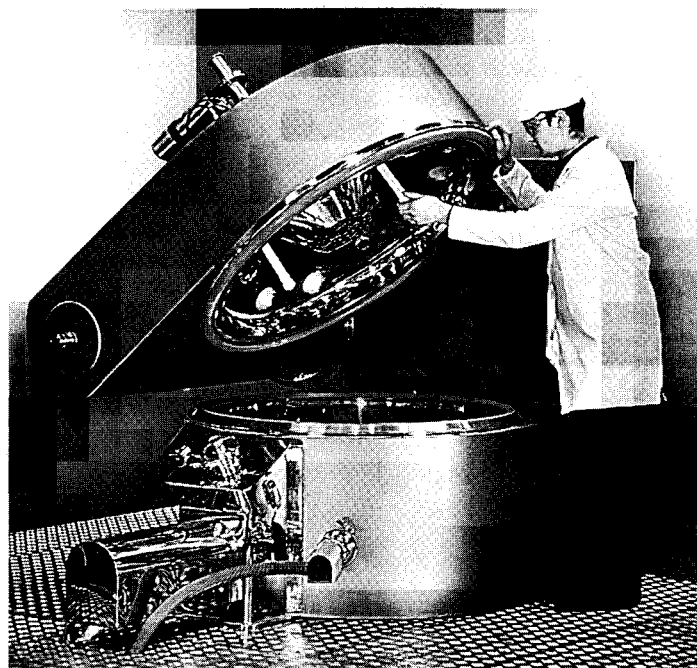


(a)



(b)

**Fig. 1** (a) Schematic view of a vertical high shear mixer (Aeromatic-Fielder, PMA); (b) schematic view of a vertical high shear mixer with horizontal chopper shaft. Microwave and vacuum systems are supplied for the drying process (Aeromatic-Fielder, Spectrum); (c) the view of a 300-L Spectrum.



(c)

Fig. 1 Continued

2. Less liquid binders are needed compared with fluid bed or low shear mixer granulators; therefore, a shorter drying process is obtained.
3. Highly cohesive materials can be granulated. In comparison these cohesive materials are difficult to fluidize and agglomerate in a fluid bed.
4. Voluminous materials can be densified by granulation.
5. The porosity of the granules can be influenced by massing time and impact of the agitators.
6. Granulation is performed in a closed system, which can include drying (microwave or vacuum) or, alternatively, transported to a fluid bed in a closed system using either gravity or vacuum transport.
7. Cleaning operation is easily done either manually or by a clean-in-place (cip) system.

The disadvantages are mainly due to the high-energy input exerted by the agitators and consequently risk of:

1. Mechanical degradation
2. Chemical degradation
3. Overwetting of product temperature
4. Producing granules with irregular shape and dissolution properties

The granulation process is influenced by many factors, including material properties and machine variables. Because of the complexity of the process, even with the best control parameters cannot be determined for fluid bed granulation, the construction of the apparatus is critical.

The basis for the development of high shear mixer granulators is the influence of the mixing action on granule growth and the influence of the drying process at least a qualitative basis.

## II. TYPES OF MIXER GRANULATORS

A list of suppliers, referring to high shear mixers, is given in Table I.

Figure 1 represents one of the types of high shear mixers. The vertical impeller is mounted on the side of the bowl. In other types the impeller is vertically mounted as shown in Fig. 2. The blades, and the chopper blades, are mounted on the impeller.

The horizontal high shear mixer rotates in a horizontal plane. The impeller is mounted along the length of the bowl. The arms are a plough-like shape. The high shear mixers are used for granulation.

The changeable bowl design allows the bowl and chopper blades being removed from the lid, as shown in Fig. 3. This allows for inspection of the shaft seal.

High shear mixers have a high energy input and are characterized as "high energy" mixers. They obtain an efficient drying process. A lower drying process is applied. A lower drying process is applied.





1. Mechanical degradation of fragile particles and granules.
2. Chemical degradation of thermolabile product owing to increase in product temperature.
3. Overwetting of the granules owing to compaction and, consequently, uncontrolled granule growth.
4. Producing granules of too low porosity, compromising tableting and dissolution properties.

The granulation process is sensitive to changes in product-, process-, and machine variables. Because high shear mixers differ much in design and specification, even within the same manufacture, a general set of process control parameters cannot be applied for the granulation process. In contrast, for fluid bed granulation, the control parameters are almost independent of the construction of the apparatus.

The basis for the development of an optimal process and formulation for high shear mixer granulation is a knowledge of the mechanisms of granule growth and the influence of product, process, and machine variables on at least a qualitative basis.

## II. TYPES OF MIXER GRANULATORS

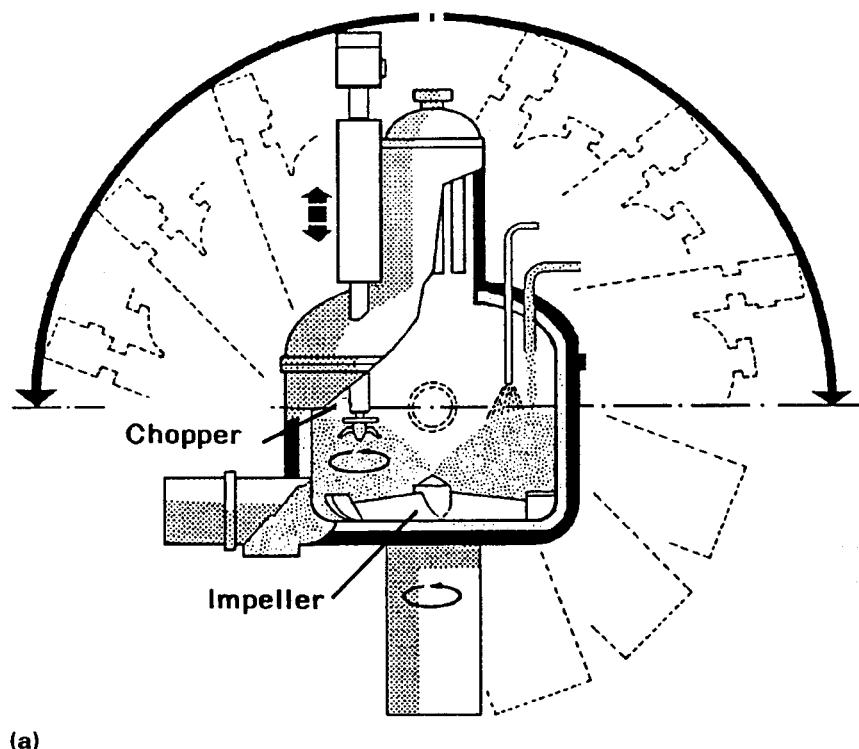
A list of suppliers, referring to the different types and specifications of high shear mixers, is given in Section XI.

Figure 1 represents one type of vertical high shear mixer, characterized by the vertical impeller shaft. The chopper is mounted horizontally in the side of the bowl. In other types of vertical high shear mixers, the chopper is vertically mounted as shown in Fig. 2. The impellers normally have three blades, and the chopper can be of a two- or multiblade type.

The horizontal high shear mixer is shown in Fig. 3. The impeller shaft rotates in a horizontal plane within a cylinder, and one or several choppers are mounted along the longitudinal direction of the cylinder. The impeller arms are a plough-like shape, and they are often referred to as the plough-share mixers.

The changeable bowl mixers are characterized by their mixing arms and chopper blades being top driven, and the shafts are mounted through the lid, as shown in Fig. 4. The top mounting of the agitators allows free inspection of the shaft seals and removal of the mixing bowl.

High shear mixers have been further developed for drying purposes, and are characterized as "single-pot process equipment," (see Fig. 1b). To obtain an efficient drying process, vacuum and microwaves in combination are applied. A lower drying capacity is obtained by external heating of the



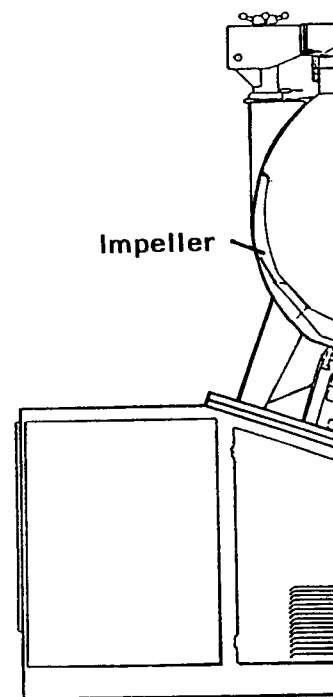
(a)

**Fig. 2** Schematic view of vertical high shear mixers with vertical chopper shaft: (a) Zanchetta, Gral with tilting bowl and retractable chopper. (b) Moritz, Turbo-sphere.

jacketed bowl in combination with vacuum and special air inlet systems through the bowl or impeller (see Chap. 10). The bowls of high shear mixers are often jacketed, because cooling during processing might be necessary owing to the high-energy input exerted by agitation. Addition of liquid binder is performed by either pumping or pouring the liquid through the lid of the mixer, or by spraying it onto the mass by a pneumatic or binary nozzle.

High shear mixers have applications other than wet granulation. The high shear mixer shown in Fig. 5 was developed specifically for melt granulation and pelletization. Pelletization can be performed by either melt or wet granulation.

When melt granulation or pelletization is performed, energy for melting the binder is supplied by agitation of the impeller and external heating of the bowl (see Sec. X). It is an advantage to have a high-energy input during melt granulation to limit the processing time. The energy input effi-

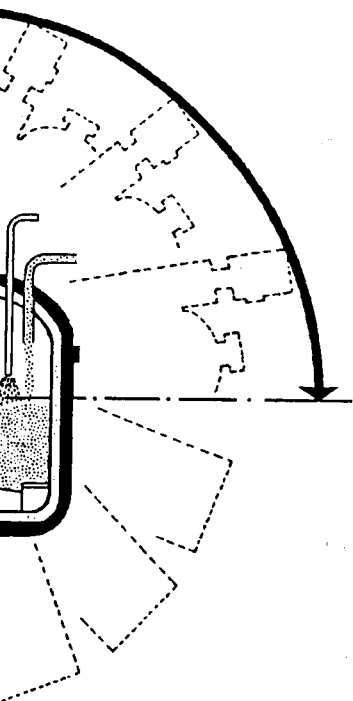


(b)

**Fig. 2** Continued

ciency of the impeller in P tional high shear mixers, o tional speed of the impeller by a rotary atomizer that binder, even if it is of very

In contrast with spray the bowl is limited, which precisely without any bias Controlling the amount of requisite for controlling the during wet massing can be overwetting and uncontrol hesion of wetted material t

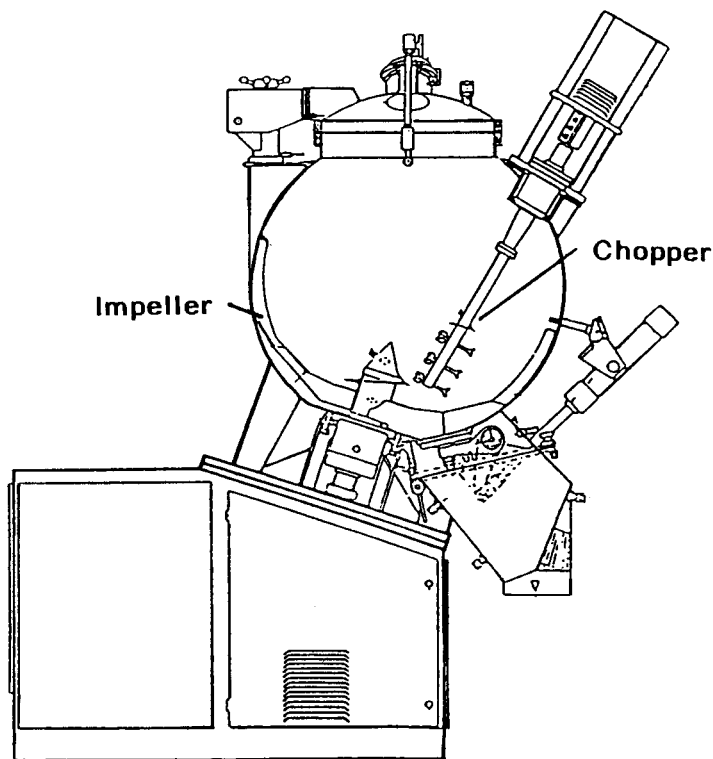


mixers with vertical chopper shaft: (a) chopper. (b) Moritz, Turbo-sphere.

m and special air inlet systems. The bowls of high shear mixers processing might be necessary agitation. Addition of liquid binder the liquid through the lid of the pneumatic or binary nozzle.

other than wet granulation. The developed specifically for melt granulation can be performed by either melt or

n is performed, energy for melt-granulation impeller and external heating might have a high-energy input during time. The energy input effi-

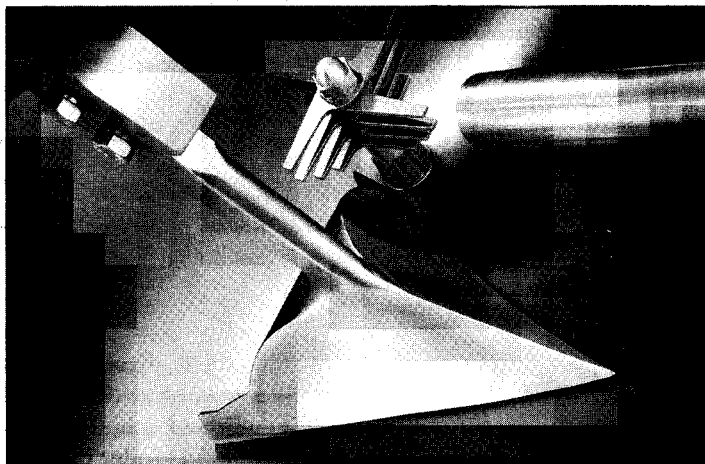
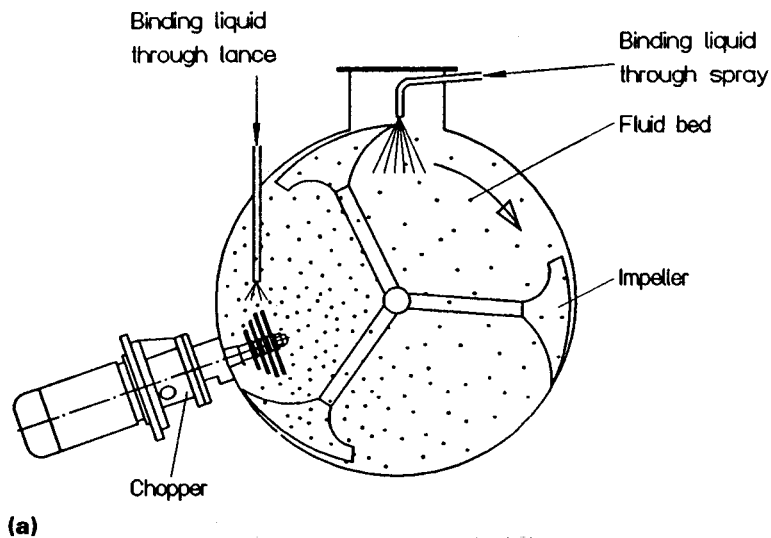


(b)

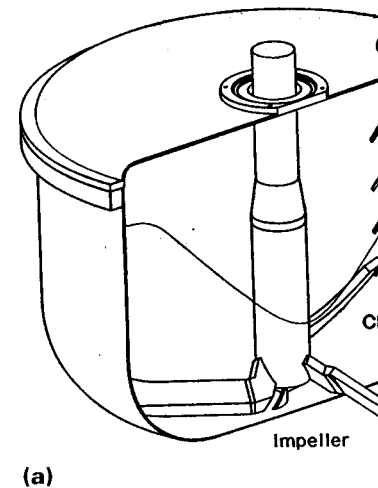
Fig. 2 Continued

ciency of the impeller in PP10 has been improved, compared with conventional high shear mixers, owing to increased blade area and a higher rotational speed of the impeller. For wet pelletization, the liquid binder is added by a rotary atomizer that allows a homogeneous distribution of a liquid binder, even if it is of very high viscosity.

In contrast with spraying by a binary nozzle, the amount of air into the bowl is limited, which means that the amount of liquid can be adjusted precisely without any bias caused by evaporation during liquid addition. Controlling the amount of liquid binder within very narrow limits is a prerequisite for controlling the wet pelletization process [4]. The rate of drying during wet massing can be controlled by a vacuum supply, which prevents overwetting and uncontrolled granule growth during wet massing [4]. Adhesion of wetted material to the wall of the bowl is minimized by an inner



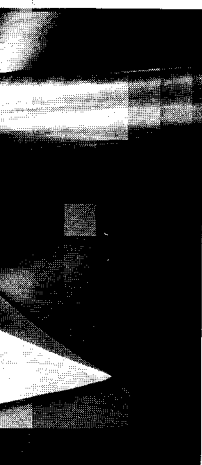
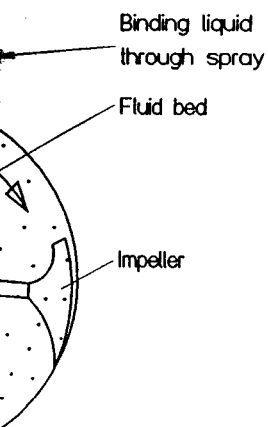
**Fig. 3** (a) Schematic view of a horizontal high shear mixer (Lödige); (b) the view inside the mixing drum shows ploughshare shovel, inlet lance for binder liquid, and multiblade chopper.



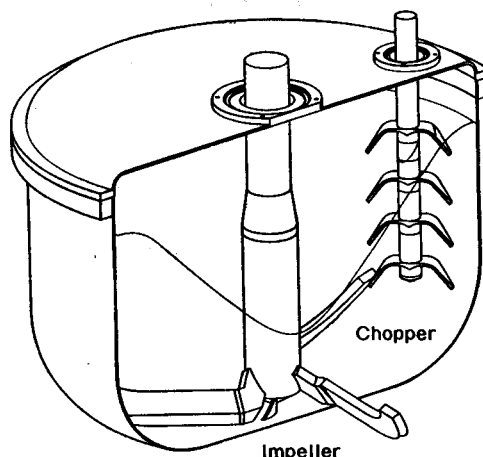
**Fig. 4** (a) Schematic view of a vertical high shear mixer (Collette, Gral); (b) view of the impeller.

polytetrafluoroethylene (PTFE) specific design improves performance for cohesive substances [4,6].

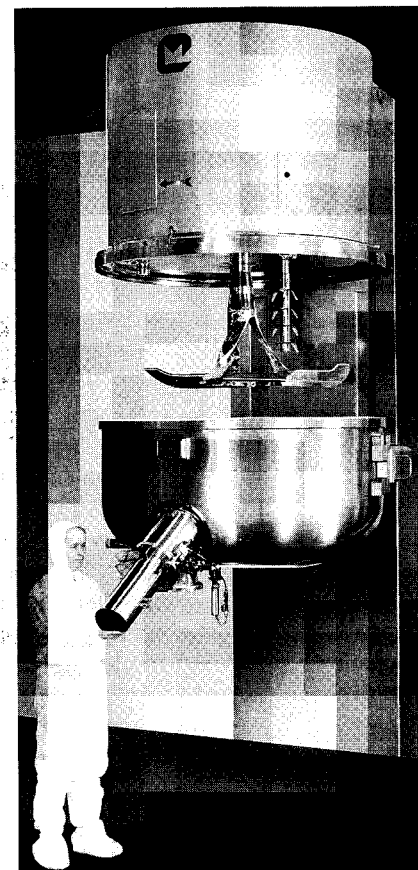
The variation in design among different types of mixers, based on size of the mixer, of high shear mixers (e.g., it can be claimed that some are classified as high shear mixers).



h shear mixer (Lödige); (b) the view  
vel, inlet lance for binder liquid, and



(a)

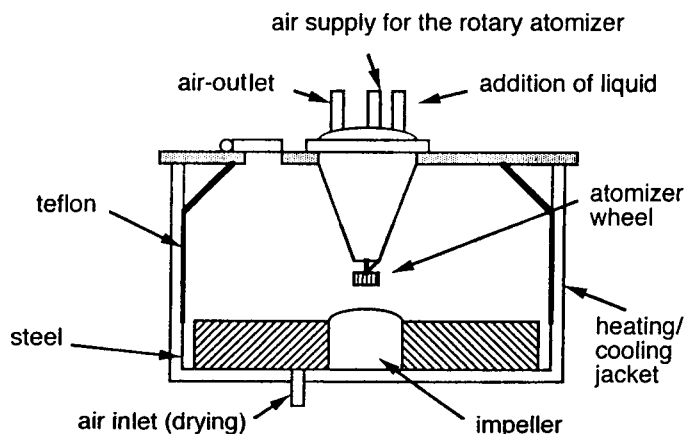


(b)

**Fig. 4** (a) Schematic view of a high shear mixer with interchangeable bowl (Machines Collette, Gral); (b) view of a 1200-L Gral.

polytetrafluoroethylene (PTFE) lining and removal of the chopper [5]. This specific design improves pelletization and granulation efficiency for highly cohesive substances [4,6].

The variation in design of impeller, chopper, and bowl is pronounced among different types of mixers and even within a manufacturer's product line, based on size of the mixer. If one compares different types and scales of high shear mixers (e.g., the power consumption and speed of agitators), it can be claimed that some have an impact capacity that is too low to be classified as high shear mixers. However, in relation to the granulation pro-



**Fig. 5** Schematic view of a high shear mixer, specifically designed for melt and wet pelletization (Aeromatic-Fielder, Pelletprocessor PP10).

cess, the most important question to raise is whether the machine has the capability of producing a satisfactory product of the specific formulation and whether the process can be scaled-up. Because the energy input requirement is dependent on the formulation to be processed, the rotational speed of the impeller and preferably chopper should at least be continuously adjustable. It is also recommended that one consider whether process-control and process-recording systems can be supplied, because these are presumably going to be the requirements of the quality control unit of any pharmaceutical company. The granulation process can be scaled up from bowl volumes of 5–10 L to 1000–3000 L in vertical high shear mixers, corresponding to batch sizes of 1 kg to a maximum of 500–1500 kg. The batch sizes of the horizontal high shear mixers can be much higher.

The granulation can be performed in a closed system. The material can be loaded by vacuum conveyor system, or by use of the vacuum supply of the mixer. After granulation, the product can be discharged through an in-line wet-sieving unit and transferred directly to a fluid bed dryer by vacuum or gravity transport.

### III. GRANULE GROWTH MECHANISMS AND GRANULATION CHARACTERISTICS

Size enlargement by agglomeration in a high shear mixer is dominated by the mechanisms of nucleation and coalescence [7]. Nucleation of particles

occurs when the surface of the binder, that liquid bridges between are resistant to the high shear forces might proceed by coalescence. Coalescence requires that the agglomerate surface plasticity to be deformed. Surface liquid is supplied by a liquid bridge between the agglomerates, squeezing them together. Because high shear forces are applied, the granulation process will be competitive (shatter and breakage). Which mechanism depends on the mechanical strength of the forces applied by the agitator and chopper. The strength of the primary particles. Thus, the material and the dominating mechanism is likely to exist as proposed.

Other factors, such as plasticity of the feed materials, mechanical impact of the agitator limits for the mechanisms of granulation. For example, particles of corn starch are round, their addition to agglomerates. A high content of crystalline cellulose contributes during the granulation process, presumably by particles mechanically stable granules of cellulose, resulting in the formation of

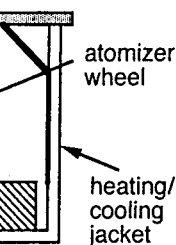
**Table 1** Relation Between Particle Size and Dominating Size Enlargement Mechanism in High Shear Mixers<sup>a</sup>

Median particle size on volume basis	Dominating Size Enlargement Mechanism
Under 20 $\mu\text{m}$	Nucleation
20–50 $\mu\text{m}$	Coalescence
Over 100 $\mu\text{m}$	Agglomeration

<sup>a</sup>Based on experiences by granulation of various materials.

ary atomizer

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impeller

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essor PP10).

is whether the machine has the  
ct of the specific formulation and  
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gh shear mixer is dominated by  
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occurs when the surface of the powder is wetted sufficiently with the liquid binder, that liquid bridges between primary particles are formed. If the nuclei are resistant to the high shear forces applied to the wet mass, granule growth might proceed by coalescence into larger agglomerates. Growth by coalescence requires that the agglomerates have excess surface liquid and sufficient surface plasticity to be deformed and to adhere at collision [8]. The free surface liquid is supplied by addition of liquid binder or by compaction of the agglomerates, squeezing the liquid to the surface of the agglomerates. Because high shear forces are applied to the agglomerates, the size enlargement process will be competitive with simultaneous degradation processes (shatter and breakage). Which one of the processes may become dominant, depends on the mechanical strength of the wet agglomerates and the shear forces applied by the agitators as related to speed and design of impeller and chopper. The strength of the wet agglomerates is dependent on the size of the primary particles. Thus, a relation between particle size of the feed material and the dominating mechanisms of size enlargement–size reduction is likely to exist as proposed in Table 1.

Other factors, such as particle shape, particle size distribution, wettability of the feed materials, surface tension of the liquid binder, and mechanical impact of the agitators, will influence which of the particle size limits for the mechanisms given in Table 1 will be dominant. To give an example, particles of corn starch have sizes of 10–20  $\mu\text{m}$ , but because they are round, their addition to a formulation may decrease the strength of the agglomerates. A high content of starch in a formulation can, therefore, result in mechanically unstable agglomerates that undergo shatter and breakage during the granulation process. In contrast, fibrous, large particles of microcrystalline cellulose contribute significantly to the strength of the agglomerates, presumably by particle-interlocking effects. This may explain why mechanically stable granules can be formed by addition of microcrystalline cellulose, resulting in the formation of pellets by wet granulation [9].

**Table 1** Relation Between Particle Size of the Feed Material and the Dominating Size Enlargement–Size Reduction Mechanism by Granulation in High Shear Mixers<sup>a</sup>

Median particle size on volume basis	Dominating size enlargement–size reduction mechanism
Under 20 $\mu\text{m}$	Coalescence, limited breakage
20–50 $\mu\text{m}$	Coalescence, breakage
Over 100 $\mu\text{m}$	Limited coalescence, shatter-breakage

<sup>a</sup>Based on experiences by granulation in Fielder PMA 25 and Diosna 25.



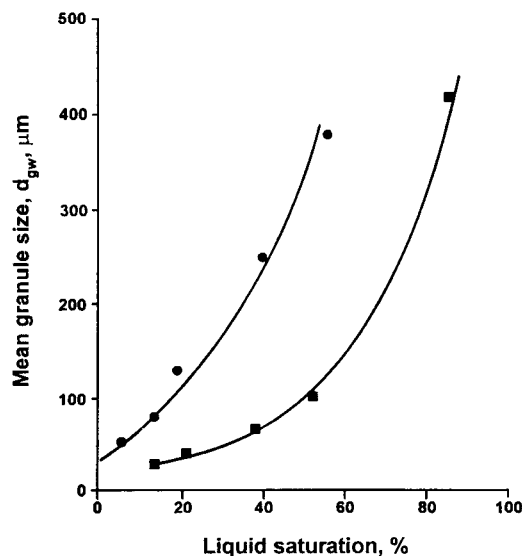


relevant examples to illustrate and their consequences for the dicalcium phosphate of the specific as a median particle size, on a basis. Lactose 200 mesh has a  $75\text{ }\mu\text{m}$  and represents a moderately fine material only used in tablet formulations. It is used in the liquid addition phase by lactose [10].

Granule growth in terms of moisture contents up to about 12%, growth by coalescence of primary particles in the dried granulate, which is reflected by an increase in granule size, as shown in Fig. 6, whereas granule growth by liquid addition of 2–3%. The increase

of mean granule size in Fig. 6 is more gradual for lactose, in comparison with the rapid increase observed for dicalcium phosphate. The differences in granule growth pattern is a consequence of the differences in agglomerate strength and the dominating size enlargement process. Dicalcium phosphate forms relatively strong agglomerates, which grow by rapid coalescence when sufficient liquid binder is present to provide the plasticity of the agglomerates. In contrast, lactose is likely to form agglomerates of lower strength owing to the larger particle size. Therefore, for lactose, granule growth by coalescence and breakage of the agglomerates are competitive processes during liquid addition; accordingly, granule growth will be more gradual compared with that of dicalcium phosphate. Because the specific surface area of lactose is lower than that of dicalcium phosphate and it possesses a high aqueous solubility, the amount of liquid binder necessary for growth by coalescence is less than that of dicalcium phosphate. The relation between the degree of liquid saturation of the agglomerates and the mean granule size describes the differences in granule growth patterns for the two materials (Fig. 7) [11].

The liquid saturation  $S$  expresses the degree of filling of the intragranular voids of the granules calculated according to Eq. (1):



**Fig. 7** Correlation between liquid saturation and mean granule size,  $d_{gw}$ , during liquid addition. For symbols see Fig. 6. (From Ref. 11.)

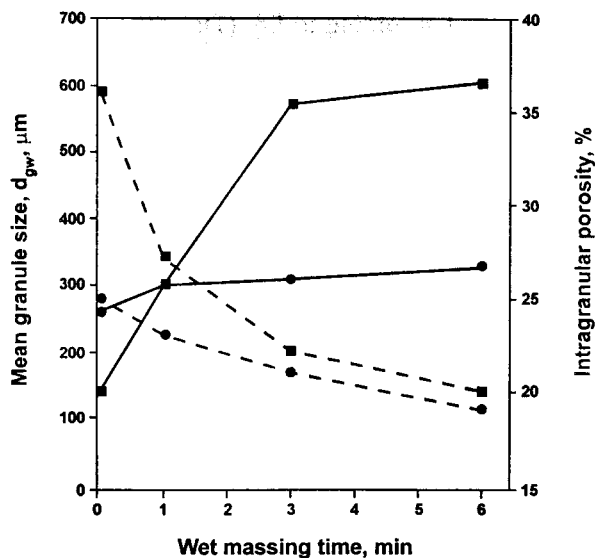
and mean granule size,  $d_{gw}$  during addition of Kollidon VA64 added by speed: 3000 rpm; ■, dicalcium phosphate; 50 g/min. High shear mixer:

$$S = \frac{H(1 - \epsilon)\rho}{\epsilon} \quad (1)$$

Where  $H$  is the moisture content on dry basis,  $\epsilon$  the granular porosity, and  $\rho$  the particle density of the feed material.

As shown in Fig. 7, lactose requires only 20–40% of liquid saturation to initiate growth by coalescence. In contrast, granule growth of dicalcium phosphate is correlated with values of liquid saturation closer to 100%. In the subsequent massing phase, the differences in granule growth pattern is even more pronounced (Fig. 8) [12].

Granule growth by coalescence proceeds for dicalcium phosphate during wet massing, whereas mean granule size is at the same level for lactose (left axis of Fig. 8). The mechanism behind this is related to the densification properties of the agglomerates [9] (Fig. 8, right axis) [13]. The granules of lactose are not significantly densified during wet massing. In contrast, a pronounced decrease in porosity is observed for the granules of dicalcium phosphate. If we again consider the low strength of lactose agglomerates, it



**Fig. 8** Correlation between wet-massing time and mean granule size,  $d_{gw}$  (left y-axis: full lines) and intragranular porosity (right y-axis: dashed lines). Liquid binder: 15% aqueous solution of Kollidon VA64. Impeller speed, 500 rpm; chopper speed, 3000 rpm; ■, dicalcium phosphate; ●, lactose. The amount of liquid binder corresponds to a moisture content of 17% for dicalcium phosphate and 8% for lactose relative to dry material. High shear mixer: Fielder PMA 25. (From Refs. 12 and 13.)

is likely that granules are formed during wet massing, equilibrating at a constant size. Granules of dicalcium phosphate are readily densified during wet massing. The granule size level will be almost constant until the liquid saturation reaches complete saturation for granule growth. Granule size increases as a result of densification and uncontrolled granule growth until the liquid saturation exceeds 100%. If the main component of a formulation is dicalcium phosphate, smaller than approximately 100 μm, comes highly critical to the formulation. For a formulation with a mean granule size of 100 μm, the strength of the agglomerates cannot be formed owing to the low strength (see Table 1). Granules can be formed only if the granule properties originate from the

#### IV. PROCESS VARIABLES

Several process variables are known to influence granulation.

- Impeller rotation speed
- Chopper rotation speed
- Load of the mixer
- Liquid addition method
- Liquid flow rate
- Wet-massing time

The effect of wet-massing time on granulation is characteristic of high shear mixer granulation. From Fig. 8 it was observed that granule size is limited for a 200-mesh lactose. This agrees with the results for lactose and corn starch, from wet massing [14–16]. The effect of liquid binder is considerable [12]; therefore, one expects granule size to increase as wet-massing time proceeds. The amount of liquid binder is a critical factor.

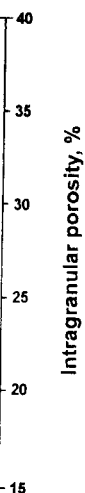
The effect of impeller speed on granulation for a cohesive formulation is also important.

(1)

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only 20–40% of liquid saturation  
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 The amount of liquid binder corre-  
 -ium phosphate and 8% for lactose  
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is likely that granules are formed and simultaneously degraded during wet massing, equilibrating at a certain level of granule size. The agglomerates of dicalcium phosphate are resistant to degradation forces and will be further densified during wet massing. In terms of the degree of liquid saturation the level will be almost constant for granules of lactose and increasing toward complete saturation for granules of dicalcium phosphate. Because liquid saturation governs granule growth (see Fig. 7), mean granule size of dicalcium phosphate increases as a result of granule growth by coalescence. Overwetting and uncontrolled granule growth occurs if wet massing is continued until the liquid saturation exceeds 100%. In agreement with this observation, if the main component of a formulation has a mean particle size, on a volume basis, smaller than approximately 10  $\mu\text{m}$ , then the granulation process becomes highly critical to the amount of liquid binder added. On the contrary, for a formulation with a mean particle size, on a volume basis, larger than 100  $\mu\text{m}$ , the strength of the agglomerates is too low, and stable agglomerates cannot be formed owing to high shear forces involved during granulation (see Table 1). Granules can be formed when the wetted mass is sieved, but the granule properties originate from the screening procedure.

#### IV. PROCESS VARIABLES

Several process variables are likely to influence the granulations process:

- Impeller rotation speed
- Chopper rotation speed
- Load of the mixer
- Liquid addition method
- Liquid flow rate
- Wet-massing time (subsequent of liquid addition time)

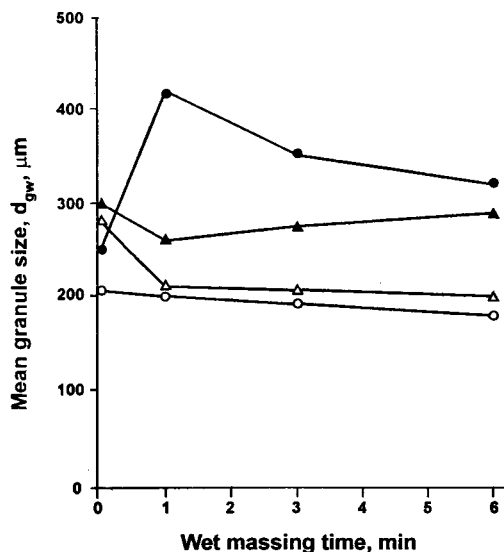
The effect of wet-massing time on granule growth depends on the granulation characteristic of the formulation, as described in Section III. From Fig. 8 it was observed that the effect of wet-massing time on mean granule size is limited for a moderately cohesive starting material, such as 200-mesh lactose. This agrees well with the result obtained by granulation of lactose and corn starch, finding no or only limited granule growth during wet massing [14–16]. The evaporation during wet massing can be considerable [12]; therefore, one expects to observe a decline in mean granule size as wet-massing time proceeds, owing to a decrease, by evaporation, in the amount of liquid binder.

The effect of impeller speed on the granulation of a moderately cohesive formulation is also limited. High impeller speed during granulation

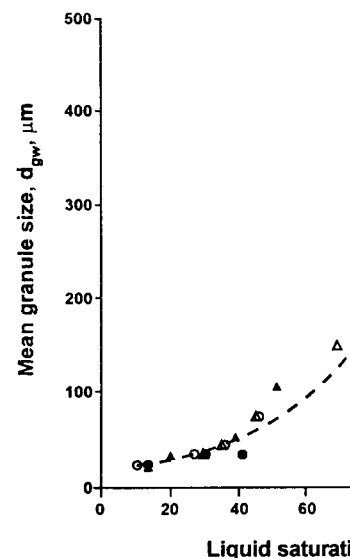
of lactose [12] or lactose in a mixture with corn starch [15–17] results in only a slight increase in mean granule size during wet massing. High impeller speed does not decrease the porosity of the lactose agglomerates [12]. It is assumed that the agglomerates of lactose require a relatively low impact to reach the minimum porosity, and that this level has already been achieved during the liquid addition phase [18].

Even a slight increase in porosity has been observed for granulating lactose and corn starch [19] at high impeller speed. Figure 9 shows the correlation between mean granule size and wet-massing time for the granulation of lactose at different impeller speeds. The mean granule size obtained during liquid addition is unchanged if the impeller speed is kept at the same level during both liquid addition and wet massing. If the impeller speed is changed, mean granule size shifts to an equilibrium level between granule growth and degradation, related to the specific rotation speed [12].

For a cohesive substance, the degree of liquid saturation governs granule growth, as shown in Fig. 10 for the granulation of dicalcium phosphate



**Fig. 9** Correlation between wet-massing time and mean granule size  $d_{gw}$  for granulation of lactose: liquid binder, 15% aqueous solution of Kollidon VA64. Amount of liquid binder corresponds to 8% moisture relative to dry material. Impeller speed during liquid addition and wet massing, respectively: ●, 250 and 500 rpm; △, 500 and 250 rpm; ▲, 500 and 500 rpm; ○, 250 and 250 rpm. High shear mixer: Fielder PMA 25. (From Ref. 12.)



**Fig. 10** Correlation between liquid saturation and mean granule size  $d_{gw}$  for the granulation of dicalcium phosphate: 15% aqueous solution of Kollidon VA64; 300 g/min; △ and ▲, spray rate 300 g/min; impeller speed 250 rpm; high shear mixer: Fielder PMA 25.

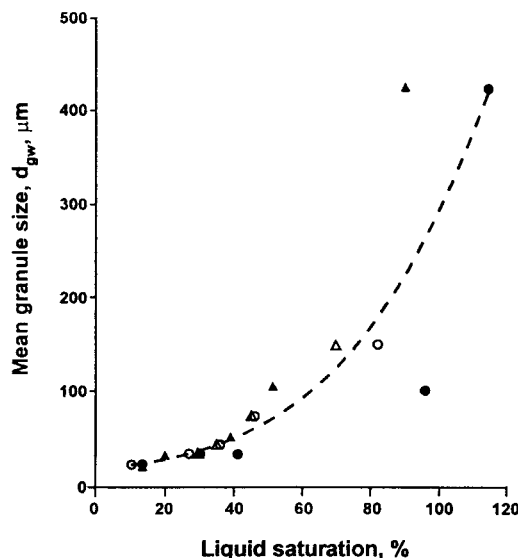
during liquid addition [11]. The effect of liquid flow rate.

A lower granule porosity is achieved at a high liquid flow rate; processing time; processing time. Figure 11 shows the granule size distribution in accordance with the theory on liquid saturation. Granule growth is obtained at a high liquid flow rate, resulting in a high liquid addition time).

The effect of wet-massing time on granule size for granulation of lactose is shown in Fig. 12 [12]. The highest granule size is obtained during wet massing, and at a high liquid flow rate, intragranular porosity were, during wet massing [13]. The effect of liquid flow rate and amount liquid binder on granule size and their effect on liquid saturation

th corn starch [15–17] results in  
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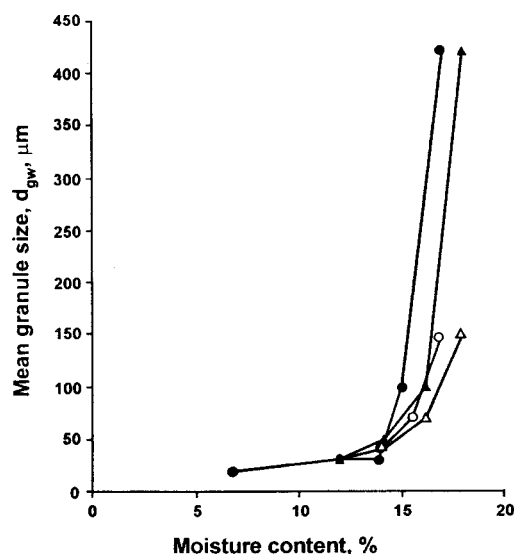
**Fig. 10** Correlation between liquid saturation and mean granule size  $d_{gw}$  during liquid addition for the granulation of dicalcium phosphate: liquid binder; 15% aqueous solution of Kollidon VA64; chopper speed: 3000 rpm; ○ and ●, spray rate 100 g/min; △ and ▲, spray rate 300 g/min; ● and ▲, impeller speed 500 rpm; ○ and △, impeller speed 250 rpm; high shear mixer: Fielder PMA 25. (From Refs. 10 and 12.)

during liquid addition [11]. The correlation is independent of impeller speed and liquid flow rate.

A lower granule porosity and, thereby, a higher degree of liquid saturation are achieved at a high level of impeller rotational speed and extended processing time; processing time being interrelated with liquid flow rate [13]. Figure 11 shows the granule growth pattern related to Fig. 10 [6]. In accordance with the theory on liquid saturation as being the controlling factor, granule growth is obtained at the lowest amount of liquid binder for the process conditions, resulting in the lowest porosity (high impeller speed and high liquid addition time).

and mean granule size  $d_{gw}$  for gran-  
solution of Kollidon VA64. Amount  
relative to dry material. Impeller speed  
actively: ●, 250 and 500 rpm; △, 500  
250 rpm. High shear mixer: Fielder

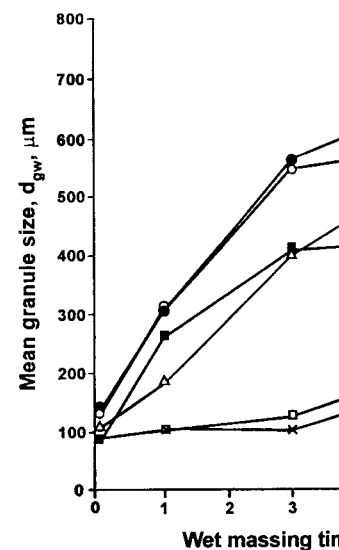
The effect of wet-massing time, impeller speed, and amount of liquid binder on granule size for granulation of dicalcium phosphate is illustrated in Fig. 12 [12]. The highest growth rate is obtained at high impeller speed during wet massing, and at a high moisture content. The lowest values of intragranular porosity were, accordingly, observed at high impeller speed during wet massing [13]. The effects of wet-massing time, impeller speed, and amount liquid binder on granule growth in Fig. 12 can be ascribed to their effect on liquid saturation, as shown in Fig. 13 [11].



**Fig. 11** Correlation between moisture content and mean granule size  $d_{gw}$  during liquid addition for the granulation of dicalcium phosphate: liquid binder, 15% aqueous solution of Kollidon VA64; chopper speed, 3000 rpm; ○ and ●, spray rate 100 g/min; △ and ▲, spray rate 300 g/min; ● and ▲, impeller speed 500 rpm; ○ and △, impeller speed 250 rpm; high shear mixer: Fielder PMA 25. (From Ref. 10.)

The method of liquid addition must be considered, because it may influence the granule size distribution of the product (Fig. 14) [10]. The lowest amount of lumps is associated with fine atomization of the liquid binder and high speed of both impeller and chopper. By pouring or pumping the liquid binder onto the powder, there is a potential risk that the overwetted lumps may be present in the product after wet massing. However, liquid distribution is improved during the subsequent wet-massing phase [12,20]. The efficiency of high shear mixers in distribution of the liquid binder is dependent on the intensity of the agitation, which is related to the speed of the agitators, their design, and the scale of equipment [21].

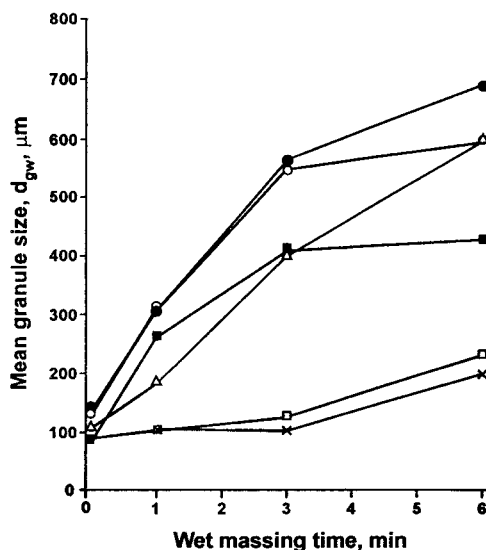
Provided that the liquid distribution is homogeneous, the effect of the chopper on granule growth and granule size distributions is limited. The chopper had no effect on mean granule size [10,12,17] when granulating lactose, lactose in mixture with corn starch, or dicalcium phosphate, were studied. However, activation of the chopper can have a narrowing effect on the granule size distribution, especially in those mixers for which the chopper is large or contributes significantly to the energy input (i.e., in Gral and



**Fig. 12** Correlation between wet massing time and mean granule size  $d_{gw}$  during liquid addition for the granulation of dicalcium phosphate: liquid binder, 15% aqueous solution of Kollidon VA64; chopper speed, 3000 rpm; to dry material); ■, □, and ×, impeller speed during liquid addition and 250 rpm; ○ and □, 500 rpm; high shear mixer: Fielder PMA 25. (From Ref. 10.)

the horizontal Lödige units). The formation of larger agglomerates at high speeds is a function of the physical properties of the starting material. The effect of the chopper on granule size distribution can be influenced by the speed of the impeller, as shown in Fig. 15.

High impeller speed and blade inclination are associated with a narrower size distribution of the final product. However, to obtain a narrow distribution, the excessive moisture must be removed. By introducing a drying phase, preventing liquid saturation from occurring, a narrow distribution can be produced for the final product. The amount of feed material in the mixer bowl's volume (15–45% w/w) does not seem to be a critical factor.



**Fig. 12** Correlation between wet-massing time and mean granule size  $d_{gw}$  for granulation of dicalcium phosphate: binder liquid, 15% aqueous solution of Kollidon VA64; chopper speed, 3000 rpm; ●, △, and ○, high moisture level (17.0% relative to dry material); ■, □, and ×, low moisture level (15.7% relative to dry material); impeller speed during liquid addition and wet-massing, respectively: × and △, 250 and 250 rpm; ○ and □, 500 and 250 rpm; ● and ■, 500 and 500 rpm; high shear mixer: Fielder PMA 25. (From Ref. 12.)

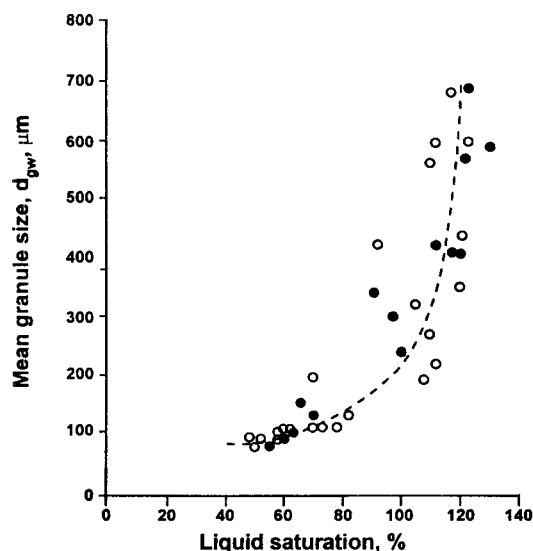
t and mean granule size  $d_{gw}$  during granulation of dicalcium phosphate: liquid binder, 15% aqueous solution of Kollidon VA64; chopper speed, 3000 rpm; ○ and ●, spray rate 100 g/min; impeller speed 500 rpm; □ and △, Fielder PMA 25. (From Ref. 10.)

be considered, because it may influence the product (Fig. 14) [10]. The degree of fine atomization of the liquid binder is influenced by the chopper. By pouring or pumping the liquid binder, there is a potential risk that the overwetted granules will be formed during wet massing. However, liquid addition during the wet-massing phase [12,20]. The granule size distribution of the liquid binder is influenced by the speed of wet-massing, which is related to the speed of the chopper [21].

If the granules are homogeneous, the effect of the chopper speed on the granule size distributions is limited. The granule size [10,12,17] when granulating dicalcium phosphate, were homogeneous, or dicalcium phosphate, were homogeneous, can have a narrowing effect on the granule size distributions. These mixers for which the chopper speed has a narrowing effect on the granule size distributions (i.e., in Gral and

the horizontal Lödige units) [21,22]. The chopper is able to comminute larger agglomerates at high speed, but the effect is dependent on the properties of the starting material [5]. However, the chopper cannot generally be used for controlling the granule size distribution. In contrast, the granule size distribution can be influenced by the speed and energy input of the impeller, as shown in Fig. 15 for the granulation of dicalcium phosphate [5].

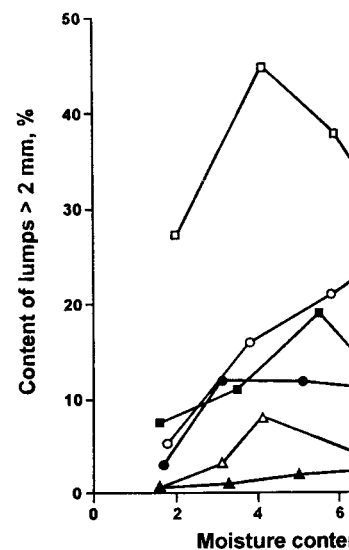
High impeller speed and high-energy input efficacy owing to high blade inclination are associated with a low standard deviation of the granule size distribution of the final product. To obtain a narrow granular size distribution, the excessive moisture formed by densification of the granules must be removed. By introducing drying air through the bowl, thereby preventing liquid saturation from exceeding 100%, narrow granule size distribution can be produced for dicalcium phosphate [4]. The load of the mixer does not seem to be a critical parameter for the granulation process [14]. The amount of feed materials normally corresponds to two-thirds of the bowl's volume (15–45% w/v) dependent on bulk volume.



**Fig. 13** Correlation between liquid saturation and mean granule size  $d_{gw}$  for the granulation of dicalcium phosphate: liquid binder, 15% aqueous solution of Kollidon VA64; chopper speed, 0 rpm or 3000 rpm. Moisture levels according to Fig. 12. Impeller speed during liquid addition and wet massing, respectively; ●, 500 and 500 rpm; ○, 500 and 250 rpm, and 250 and 250 rpm; high shear mixer: Fielder PMA 25. (From Ref. 11.)

From the foregoing examples, it can be concluded that the main process parameters of influence on mean granule size, size distribution, and granule porosity are impeller speed, wet-massing time, and total-processing time. Only these process variables have a major influence on cohesive formulations that undergo densification during granulation, and the quantitative effects are dependent on design of the impeller, scale of the mixer, and the mixer type [21,22]. To prevent inhomogeneous liquid distribution, which may give rise to lumps in the end product, it is recommended that the liquid binder be added by fine atomization instead of pouring it into the bowl within a short time period.

The droplet size of liquid binder does not directly affect the granule size, as for granulation in a fluid bed [10]. Sufficient atomization can be achieved by pressure nozzles when adding the liquid to the dry binder or a binary nozzle when binder solutions are used. The operations following the granulation process (i.e., wet-sieving and dry-sieving) may change the granule size distribution significantly and affect the bulk properties and tableting properties of the granulate [23].



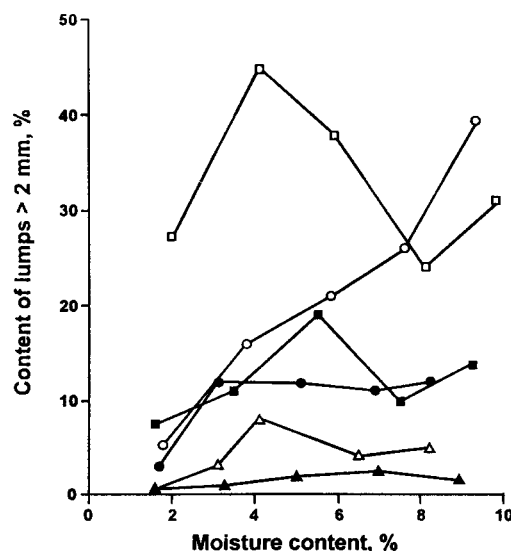
**Fig. 14** Correlation between moisture content and content of lumps over 2 mm for the granulation of dicalcium phosphate: liquid binder, 15% aqueous solution of Kollidon VA64; chopper speed, 0 rpm or 3000 rpm. Moisture levels according to Fig. 12. Impeller speed during liquid addition and wet massing, respectively; ●, 500 and 500 rpm; ○, 500 and 250 rpm, and 250 and 250 rpm; high shear mixer: Fielder PMA 25. (From Ref. 10.)

## V. PRODUCT VARIABLE

As described in Sections III and IV, the process variables have a significant effect on the product. The following variables might influence the product:

1. Amount of liquid binder
2. Characteristics of the liquid binder
  - Surface tension
  - Viscosity
  - Adhesiveness
3. Characteristics of the granule
  - Particle size and distribution
  - Particle specific surface area
  - Solubility in the liquid binder





**Fig. 14** Correlation between moisture content during liquid addition and content of lumps over 2 mm for the granulation of lactose: liquid flow, 50 g/min; liquid binder, 15% aqueous solution of Kollidon VA64; ○, ●, ■, and □, without atomization of liquid binder; △ and ▲, with fine atomization of liquid binder; ○, ●, △, and ▲, impeller speed 500 rpm; ■ and □, impeller speed 250 rpm; ●, ■, and ▲, chopper speed 3000 rpm; ○, △, and □, without chopper action; high shear mixer: Fielder PMA 25. (From Ref. 10.)

## V. PRODUCT VARIABLES

As described in Sections III and IV, the particle size of the starting materials has a significant effect on how critical the granulation process is to amount of liquid binder, wet-massing time, and impeller speed. Many other product variables might influence the granulation process; namely,

1. Amount of liquid binder
2. Characteristics of the liquid binder
  - Surface tension
  - Viscosity
  - Adhesiveness
3. Characteristics of the feed materials
  - Particle size and size distribution
  - Particle specific surface area
  - Solubility in the liquid binder



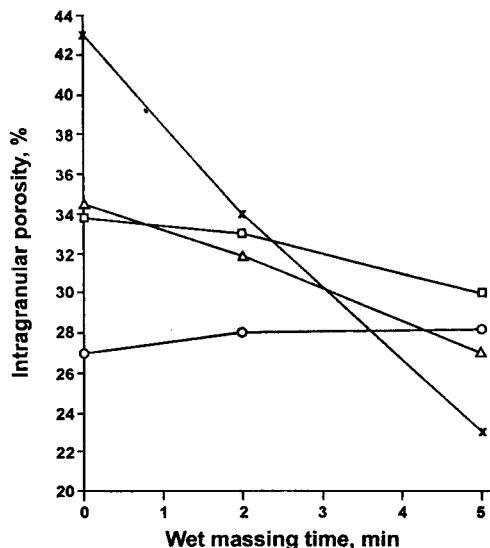
different grades of dicalcium phosphate, owing to the different granule porosities obtained. Formulations with lactose are agglomerated at degrees of liquid saturations lower than 70%, irrespective of particle size.

The liquid requirement was dependent on particle size [18,20,25]. When the particle size of lactose was decreased, an increasing amount of binder solution was needed to achieve a particular granule size [18,20,25]. In contrast to the results obtained with different particle sizes of dicalcium phosphate, the correlation between liquid saturation and mean granule size was independent of the particle size of lactose [18]. The different liquid requirements, therefore, were due to different densification properties of the lactose grades. Changes in particle size from batch to batch or the process conditions have the most influence on granulation of cohesive formulations. The robustness of the granulation process might be improved by increasing the particle size of the cohesive components, or by adding excipients that facilitate the densification process. The addition of corn starch to dicalcium phosphate [18,26,27] improved the rate of consolidation so that the minimum granular porosity was achieved early in the wet-massing phase (Fig. 16).

ometric standard deviation ( $s_g$ ) of the dicalcium phosphate: liquid binder, miller blade inclination: 30°, ▲ and △; 0 rpm, ■, ▲, and ●; impeller speed PMA 25. (From Ref. 5.)

quality, requires a knowledge of granule properties of changes in materials (i.e., specific surface area for a specific formulation is un- the relation between mean gran- of the agglomerates. The particle and the agitation energy needed to and, therefore, the liquid satura- red to obtain granule growth is

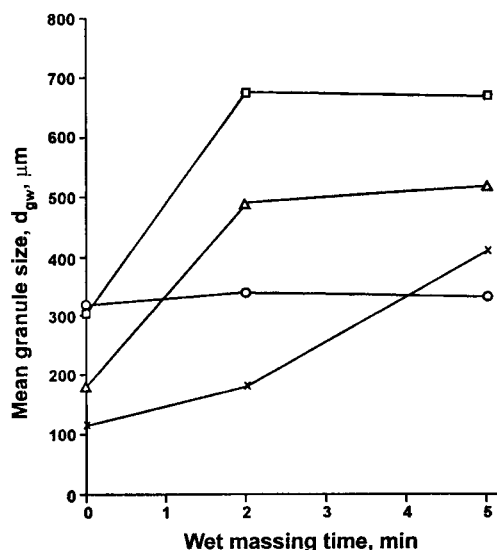
By agglomeration of different as found that by increasing the imately 30  $\mu\text{m}$  and in doing so e growth by coalescence was 50%. Surprisingly, the liquid re- ce was at the same level for the



**Fig. 16** Correlation between wet-massing time and intragranular porosity: binder liquid, 15% aqueous solution of Kollidon VA64; impeller speed, 250 rpm; chopper speed, 3000 rpm; starting materials: ○, lactose, ×, dicalcium phosphate; △, dicalcium phosphate; □, dicalcium phosphate/corn starch 85/15 w/w ratio; ◻, dicalcium phosphate/corn starch 55/45 w/w ratio; high shear mixer: Fielder PMA 25. (From Ref. 26.)

It is likely that the rounded shape of corn starch particles aids the densification during liquid addition; therefore, a lower granule porosity is obtained at the end of liquid addition compared with the formulation of dicalcium phosphate. Consequently, a more gradual increase in liquid saturation of the agglomerates is obtained during wet massing, and the increase in mean granule size is easier to control. This is shown in Fig. 17, indicated by the constant level of granule size obtained during wet massing for the formulations with corn starch, whereas granule growth proceeds only for the formulation comprising dicalcium phosphate.

A similar effect is assumed to be obtained by incorporating microcrystalline cellulose (MCC) into a cohesive formulation. Moreover, MCC contributes to the strength of the wet agglomerates and by plasticizing the mass, granules can be spheronized. Narrow granule size distributions of microgranules [28] and pellets [29] can thereby be obtained by granulation in a high shear mixer. Importantly, the liquid requirement is dependent on the densification of the agglomerates which, in turn, is affected by the impact of the agitators related to type and scale of high shear mixer [21,22,30,31].

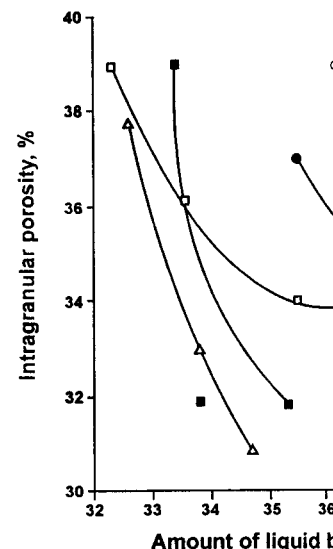


**Fig. 17** Correlation between wet-massing time and mean granule size  $d_{gw}$ : binder liquid, 15% aqueous solution of Kollidon VA64; impeller speed, 250 rpm; chopper speed, 3000 rpm; starting materials: ○, lactose; ×, dicalcium phosphate; △, dicalcium phosphate/corn starch 85/15 w/w ratio; □, dicalcium phosphate/corn starch 55/45 w/w ratio; high shear mixer: Fielder PMA 25. (From Ref. 26.)

The amount of liquid binder required for moisture-activated granulation is dependent on the amount of drug substance, a binder, and a moisture-absorbing material. The amount of liquid binder required to absorb any excessive moisture is dependent on the amount of drug substance, a binder, and a moisture-absorbing material.

The effects on granule growth of binder, surface tension, and viscosity were investigated by granulation of a drug substance with a viscosity (5–120 mPa) and a surface tension effect on granule growth. The amount of granule size was independent of the surface tension of the binder solution. The amount of granule size addition is affected by the surface tension of the binder solution, as is demonstrated in Fig. 18.

The surface tension of a drug substance in ethanol to the aqueous solution is dependent on the amount of drug substance, a binder, and a moisture-absorbing material.



**Fig. 18** Correlation between intragranular porosity and amount of liquid binder during liquid addition for the granulation of a drug substance with a viscosity of 90; solution media, water or methanol; surface tension of the binder solution, 60 mN m<sup>-1</sup>; liquid binders (10<sup>-3</sup> N m<sup>-1</sup>); 60 mN m<sup>-1</sup>; high shear mixer: Fielder PMA 25. (Unpublished data.)

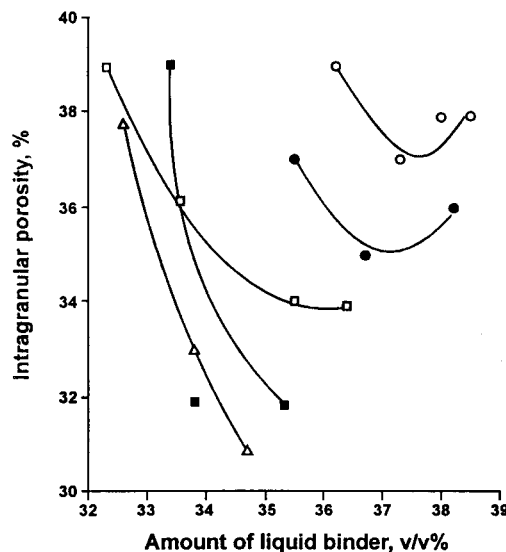
of corn starch particles aids the  
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in turn, is affected by the impact  
high shear mixer [21,22,30,31].

The amount of liquid binder can be reduced significantly by applying moisture-activated granulation principles to the high shear mixer [32]. By this process, a low amount of water (1–4%) is added to a mixture of the drug substance, a binder, and eventually, a filler. In the next stage, a moisture-absorbing material is mixed with the moistened agglomerates to absorb any excessive moisture.

The effects on granule growth and liquid requirement of the type of binder, surface tension, and viscosity of the binder solution have been investigated by granulation of dicalcium phosphate [33]. It was concluded that the viscosity (5–120 mPa) of different binder solutions alone has a slight effect on granule growth. The correlation between liquid saturation and mean granule size was independent of type of binder and viscosity and surface tension of the binder solution. However, the change in porosity during liquid addition is affected by the surface tension of the binder solution. This effect is demonstrated in Fig. 18.

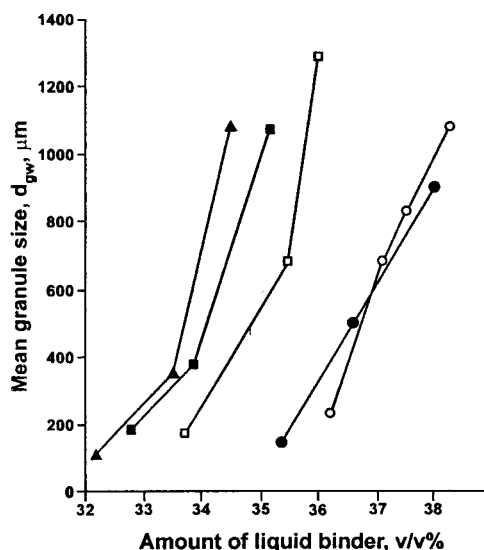
The surface tension of a solution of Kollidon 90 was varied by addition of ethanol to the aqueous media, and different densification levels were



**Fig. 18** Correlation between amount of binder liquid and intragranular porosity during liquid addition for the granulation of dicalcium phosphate: binder, Kollidon 90; solution media, water or mixtures of water and ethanol; surface tensions of the liquid binders ( $10^{-3}\text{N m}^{-1}$ ): 69,  $\Delta$ ; 53,  $\blacksquare$ ; 42,  $\square$ ; 25,  $\bullet$ ; 20,  $\circ$ ; high shear mixer: Fielder PMA 25. (Unpublished results, P. Holm.)

and mean granule size  $d_{gw}$ : binder  
impeller speed, 250 rpm; chopper  
dicalcium phosphate;  $\Delta$ , dicalcium  
dicalcium phosphate/corn starch 55/45  
From Ref. 26.)

obtained during liquid addition. The lowest porosity value was obtained for the liquid binder of the highest surface tension. Enhanced surface tension is associated with stronger liquid bondings between primary particles [34], which apparently aids the densification of the agglomerates. Because the correlation between liquid saturation and mean granule size is consistent [33], the liquid requirement to achieve granule growth is dependent on the surface tension of the binder solution, as shown in Fig. 19. The effects of surface tension on granule porosity and liquid requirements are confirmed for aqueous solutions of binders such as hydroxypropyl methyl cellulose (HPMC), polyvinyl pyrrolidone (PVP), and polyvinyl alcohol (PVA)-PVP [33]. Protein-S (hydrolyzed gelatin) differs from these binders in giving rise to granule growth at an amount of liquid binder that is lower than expected. From empirical knowledge, the adhesion properties of binders are different. This means that the deposition of stationary wetted material within the mixing bowl can be affected by the choice of binder. As an example, PVP 90 resulted in a significantly higher amount of deposited material granulating dicalcium phosphate than Protein-S or PVA-PVP (Kollidon VA64) (unpub-



**Fig. 19** Correlation between amount of bladder liquid and mean granule size  $d_{gw}$  during liquid addition for the granulation of dicalcium phosphate: binder, Kollidon 90; solution media, water or mixtures of water and ethanol; surface tensions of the liquid binders ( $10^{-3}\text{N m}^{-1}$ ): 69,  $\Delta$ ; 53,  $\blacksquare$ ; 42,  $\square$ ; 25,  $\bullet$ ; 20,  $\circ$ ; high shear mixer: Fielder PMA 25. (Unpublished results, P. Holm.)

lished results, P. Holm). Deposition in the bowl is often a problem for granulation by centrifugal forces exerted on the granules during the formulation by addition of liquid.

The binder is often dry and must be dissolved in a solution. This method is not always effective, as the binder might not be dissolved and the granules might not grow, especially if the liquid is poor. However, contrary, if it is assured that the binder is dissolved, liquid addition, it is more effective. The granule size by using a pressure nozzle. The granule size (amount of lumps) is dependent on the binder solution [20,35,36]. As a result of the effect of formulation parameters, this cannot solely be explained by granulation. Because of the many variables of the multivariate type will be studied. Development of a specific component. Proposals for experimental design are found in the statistical literature.

## VI. APPARATUS VARIATION

The degree of impact on the granules are dependent on the mixer characteristics. The size and shape of the chopper differ in different high shear mixers, the flow of material depends on the pattern created? The flow pattern created by the mixer (Pelletprocessor, PP1) is different following the movement of the granules. The normal cylindrical bowl is not suitable for inspection through the wall. The granules from a side view when the granules are accelerated up (the granulation zone), creating a space. Behind this zone, the granules are decelerated by frictional forces. The granules next impeller blade. A cross-section of the granules is shown in Fig. 21. The active granulation area is a triangular area at the tip of

est porosity value was obtained for  
 ension. Enhanced surface tension is  
 s between primary particles [34],  
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 d mean granule size is consistent  
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 s shown in Fig. 19. The effects of  
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 s hydroxypropyl methyl cellulose  
 and polyvinyl alcohol (PVA)-PVP  
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 binder that is lower than expected.  
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 ry wetted material within the mix-  
 of binder. As an example, PVP 90  
 of deposited material granulating  
 VA-PVP (Kollidon VA64) (unpub-

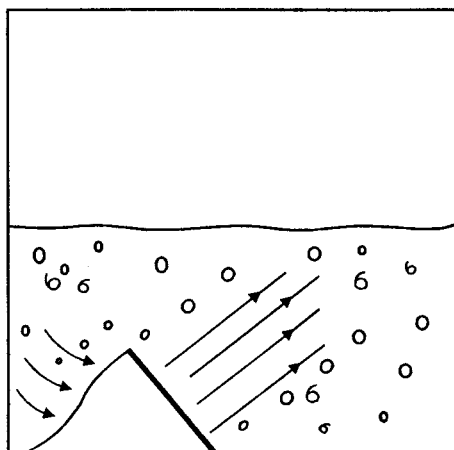
lished results, P. Holm). Deposition of moistened material on the wall of the bowl is often a problem for cohesive formulations owing to the high centrifugal forces exerted on the wetted mass by the agitators. Modification of the formulation by addition of starch might reduce this problem [18].

The binder is often dry blended to save the preparation of a binder solution. This method is not generally recommended because the binder might not be dissolved and homogeneously distributed during processing, especially if the liquid is poured onto the mass over a short time. On the contrary, if it is assured that the dry binder reaches a dissolution stage during liquid addition, it is more convenient to atomize the solvent for the binder by using a pressure nozzle. The granule property (e.g., mean granule size, amount of lumps) is dependent on whether the binder is added dry or as a binder solution [20,35,36]. Although many reports in the literature describe the effect of formulation parameters on granule growth and granule properties, this cannot solely be the basis for the development of a new formulation. Because of the many factors involved, only an experimental design of the multivariate type will provide the information necessary for development of a specific composition and optimization of granule properties. Proposals for experimental designs have been given [37-40] or can be found in the statistical literature.

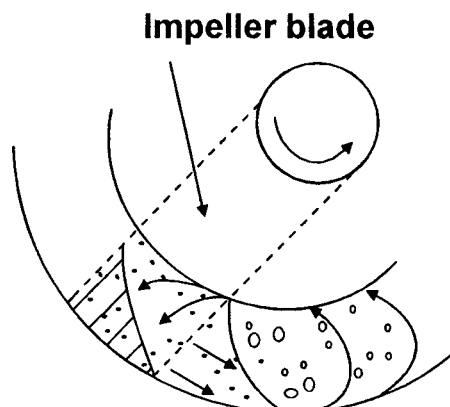
## VI. APPARATUS VARIABLES

The degree of impact on the mass and the flow pattern of the wetted material are dependent on the mixer construction, with an effect on the granulation characteristics. The size and shape of the mixing chamber, impeller and chopper differ in different high shear mixers. In the vertical high shear mixers, the flow of material describes a toroidal movement. How is this flow pattern created? The flow pattern within the mixing bowl of a high shear mixer (Pelletprocessor, PP1-prototype) was examined by a video camera, following the movement of dry pellets labeled with a luminescent agent. The normal cylindrical bowl of steel was changed to a glass bowl, allowing inspection through the wall. Figure 20 shows the flow direction of the pellets from a side view when the tip of one of the impeller blades is passing. The particles are accelerated upward and forward by the impeller blade (activation zone), creating a space free of particles on the back side of the blade. Behind this zone, the particles are falling to the bottom of the bowl, being decelerated by frictional forces (deactivation zone), ready to be hit by the next impeller blade. A cross section of the flow pattern from a top view is shown in Fig. 21. The active zone of the impeller blade is located on a small triangular area at the tip of the blade (hatched). The area of particles being

lder liquid and mean granule size  $d_{gw}$   
 dicalcium phosphate: binder, Kollidon  
 r and ethanol; surface tensions of the  
 , □; 25, ●; 20, ○; high shear mixer:  
 m.)



**Fig. 20** Side view of a cylindrical bowl indicating the flow direction of granulated materials affected by a rectangular flat impeller blade. (Based on instant video recordings). (Unpublished results, P. Holm and J. Schröder.)



**Fig. 21** Top view of a cylindrical bowl indicating the flow direction of granulated materials affected by a rectangular flat impeller blade (based on instant video recordings): hatched, active zone of impeller blade; dots, activated zone of particles; circles, deactivated zone of particles. (Unpublished results, P. Holm and J. Schröder.)

activated is marked with dots and moves upward until they fall down towards the center of the bowl to be activated again. The particles will experience impact, centrifugal, centripetal forces. The impeller blade will be active during the granulation process. However, as the mass is densified, only the outer layer is active. This means that even though the blade tips have a significant effect on granule porosity was obtained.

The effect of varying the speed of the 25-L vertical Fielder Mixer was studied. The mixers were constructed, as illustrated in Fig. 22, and the angle of inclination of the bowl was varied on granule size distribution. The effect of granular porosity was obtained.

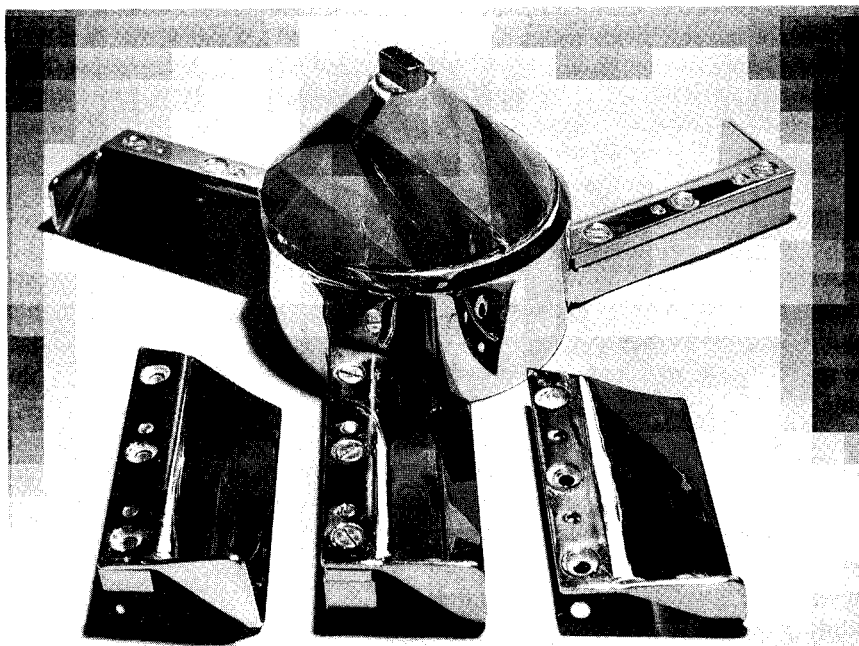


**Fig. 22** Design of changeable mixer. (From Ref. 5.)

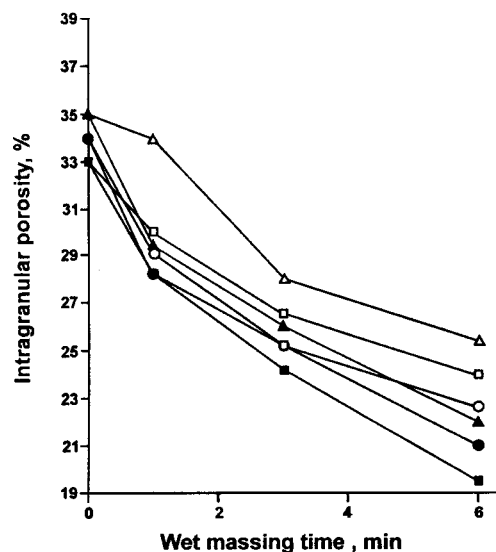


activated is marked with dots. In front of this zone the particles are pushed upward until they fall down by gravity and, thereby, are forced toward the center of the bowl to be activated again; thus, the toroidal flow pattern is created. The particles will experience high-velocity gradients owing to direct impact, centrifugal, centripetal, and frictional forces. A larger part of the impeller blade will be active in the mixing stage and liquid addition part of the granulation process. However, in the wet-massing phase in which the mass is densified, only the small triangular area near the tip of the blade is active. This means that even a small change in shape, size, or inclination of the blade tips have a significant effect on the impact of the mass.

The effect of varying the impeller blade inclination was examined in 25-L vertical Fielder Mixer [5]. Three different changeable impeller blades were constructed, as illustrated in Fig. 22. The blade area was kept constant, and the angle of inclination varied by levels of 30°, 40°, and 50°. The effect on granule size distribution was described previously (see Fig. 15) and the effect on granular porosity is shown in Fig. 23. It appears that the lowest granule porosity was obtained at high impeller speed, with blade angles of



**Fig. 22** Design of changeable impeller blades in a Fielder PMA 25 high shear mixer. (From Ref. 5.)



**Fig. 23** Effect of wet-massing time on intragranular porosity of the granules for the granulation of dicalcium phosphate: liquid binder, 15% aqueous solution of Kol-lidon VA64; impeller blade inclination: 30°, ▲ and △; 40°, ○ and ●; 50°, ■ and □; impeller speed 400 rpm, ■, ▲, and ●; impeller speed 200 rpm, ○, △, and □; high shear mixer: Fielder PMA 25. (From Ref. 5.)

40° and 50°. The effect can be explained by the difference in vertical height of the impeller blade, or as the difference in relative swept volume. The vertical volume swept out by one impeller blade at each revolution is calculated by dividing the blade area into vertical segments. Based on this volume and the impeller speed, the volume swept out by the three blades per second is determined relative to the volume of the bowl, as shown in Table 2.

When the relative swept volume is large, it reflects a high impact on the granules and, consequently, the lowest porosity was found at a high impeller speed combined with high blade inclination (see Fig. 23). The relative swept volume is correlated with energy input as indicated by the increase in product temperature given in Table 2. A comparison of different impellers with two or three flat rectangular blades and inclinations (20°, 30°, and 40°) was made in a prototype of Pelletprocessor, PP1. The comparison was based on the wet pelletization efficiency of a formulation containing a mixture of lactose and microcrystalline cellulose. The power consumption of the mixer motor was monitored during the wet-massing phase of 15 min.

**Table 2** Relative Swept Volume for Different Impeller Configurations and Product Temperature after 6 min of Wet Massing. Impeller: Fielder PMA 25

Impeller blade angle (degrees)	Relative Swept volume (s <sup>-1</sup> )
30	2.20
40	2.82
50	3.36

Source: Ref. 5.

Pelletization experiments were conducted at impeller speeds of 400–1200 rpm). The comparison of different impeller configurations was made during wet massing by measuring power consumption recorded on the blade inclination (20°) no pellets were formed. For the two-bladed impeller, the values of geometric standard deviations of 30° and 40°, as shown in Table 2, standard deviation of the geometric standard deviation of the geometric standard deviation is illustrated at two levels of 10% and 20%.

The pellet quality was evaluated by measuring the blades from two to three. The input is not the only parameter for the characteristics, other factors must be taken into account. The blades, must be taken into account of the mixing tools was previously constructed of the standard construction of the standard. Furthermore, a specially constructed mixer, as shown in Figure 1, was used for the same mixer, as shown in Figure 1.

The specialized tools were used for the granulation efficiency. Adhesion of wetted mass on the bowl was markedly lower. The results were significantly lower and the specialized tools seem to be more efficient [22]. Use of the specialized tools results; therefore, it is assumed that the granulation efficiency.

**Table 2** Relative Swept Volume for Different Impeller Configurations and Product Temperature Increase During 6 min of Wet Massing. Impeller Speed: 400 rpm. Fielder PMA 25

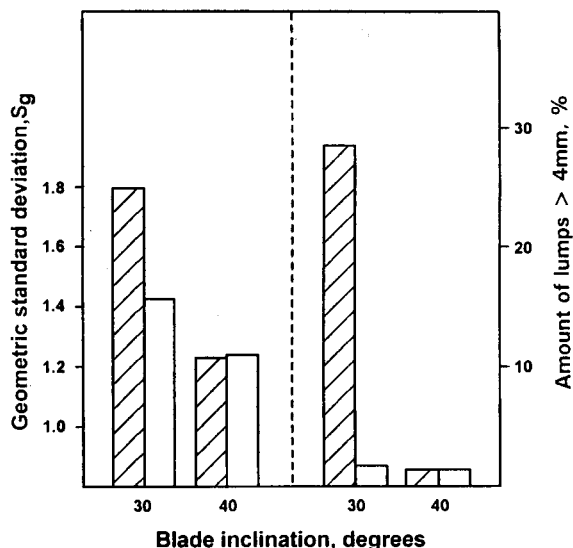
Impeller blade angle (degrees)	Relative Swept volume ( $s^{-1}$ )	Temperature increase ( $^{\circ}C$ )
30	2.20	24.8
40	2.82	31.3
50	3.36	38.0

Source: Ref. 5.

Pelletization experiments were performed at different impeller speeds (400–1200 rpm). The comparison of pellets characteristics for the different impeller configurations were performed at the same level of energy input during wet massing by method of interpolation between different integrated power consumption recordings during wet massing. At the lowest angle of blade inclination ( $20^{\circ}$ ) no pellets were formed with the three-bladed impeller. For the two-bladed impeller, the lowest amount of lumps and the lowest values of geometric standard deviation (Sg) were found for the blade inclinations of  $30^{\circ}$  and  $40^{\circ}$ , as shown in Fig. 24. The comparison of the geometric standard deviation of the granule size distribution and amount of lumps is illustrated at two levels of energy input.

The pellet quality was not improved by increasing the number of blades from two to three. In summary, it was concluded that the energy input is not the only parameter with influence on granule growth and granule characteristics, other factors, such as number of blades and inclination of the blades, must be taken into consideration. The effect of the construction of the mixing tools was proved in a vertical 25-L Diosna mixer [22]. The construction of the standard impeller and chopper is shown in Fig. 25. Furthermore, a specially constructed impeller and chopper were used in the same mixer, as shown in Fig. 26 [5].

The specialized tools were significantly better than the standard one. Adhesion of wetted mass (dicalcium phosphate) to the wall and the lid of the bowl was markedly lower, which might be why the amount of lumps were significantly lower and granule size distribution narrower. Thus, the specialized tools seem to result in a more regular movement of the mass [22]. Use of the specialized impeller without the chopper gave similar results; therefore, it is assumed to be the design of the impeller that improved the granulation efficiency.

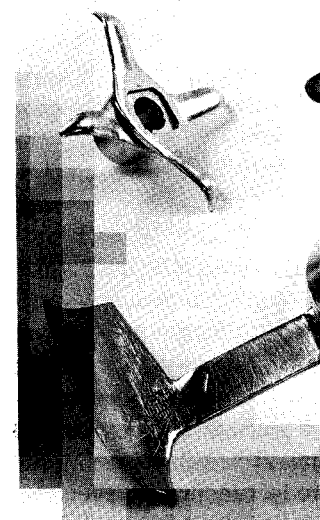


**Fig. 24** Comparison of a two-bladed impellers of 30° and 40° blade inclination for their effect on granule size distribution (geometric standard deviation, left axis) and amount of lumps larger than 4 mm in the final product (right axis). The comparison is made on basis on equal energy input during wet massing (15 min). Energy input: 150 kJ, diagonal-lined bars; 210 kJ, open bars; high shear mixer: Prototype of Pelletprocessor, PP1. (Unpublished results, P. Holm and J. Schroeder.)

The effect of the chopper on granulation is contradictory. In the 25-L Fielder mixer, two choppers of different sizes were investigated as shown in Fig. 27. Neither chopper size nor chopper rotation speed had any effect on granule size or size distribution [5], provided the liquid distribution was homogeneous. The chopper had an effect on the flow pattern of the mass by disturbing the toroidal movement. In other mixers (Lödige FM50 horizontal, Diosna 25-L, and Gral 300), chopper speed affected granule growth and granule size distribution [21,22]. It is likely that the choppers in these mixers have an impeller-like effect owing to their size or placement and, therefore, affect the granular porosity and granule growth [22]. It has been claimed that the multibladed chopper, on which the blades are parallel to the wall of the bowl ("christmas tree-like") is more effective compared with the design shown in Fig. 27, but no experimental evidence has been given. The adhesion of wetted material to the wall of the bowl can be significant [5,18], especially for the granulation of a highly cohesive material. Deposition of wetted material results in uneven liquid distribution, and



**Fig. 25** Standard impeller and



**Fig. 26** Specialized impeller

Amount of lumps > 4mm, %

30

20

10

ers of 30° and 40° blade inclination  
ometric standard deviation, left axis)  
final product (right axis). The com-  
during wet massing (15 min). Energy  
en bars; high shear mixer: Prototype  
P. Holm and J. Schroeder.)

tion is contradictory. In the 25-L  
sizes were investigated as shown  
per rotation speed had any effect  
provided the liquid distribution was  
on the flow pattern of the mass  
other mixers (Lödige FM50 hori-  
er speed affected granule growth  
likely that the choppers in these  
g to their size or placement and,  
granule growth [22]. It has been  
which the blades are parallel to  
ce'') is more effective compared  
experimental evidence has been  
to the wall of the bowl can be  
lation of a highly cohesive mate-  
in uneven liquid distribution, and

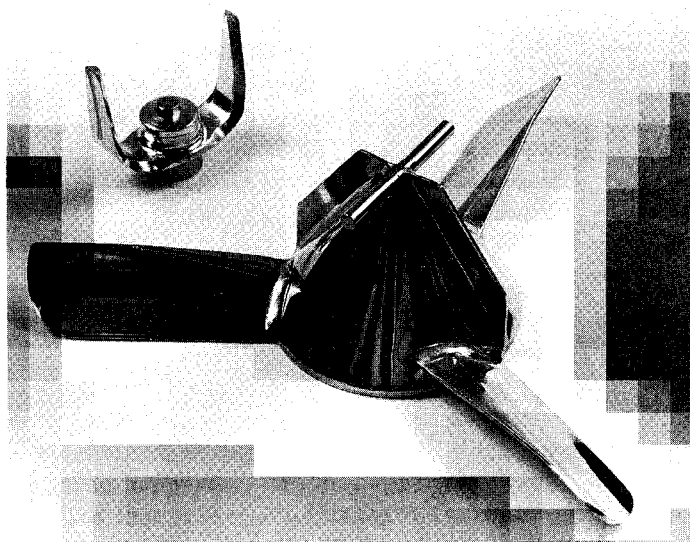


Fig. 25 Standard impeller and chopper of Diosna 25. (From Ref. 22.)

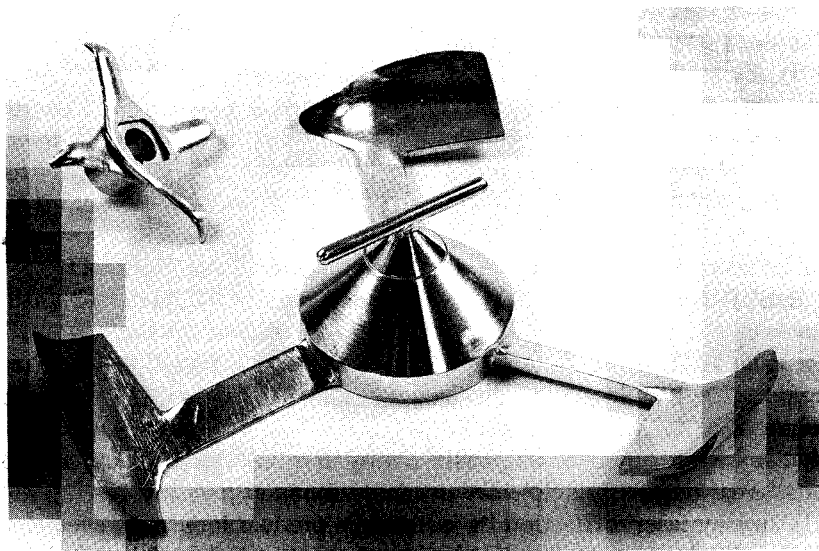


Fig. 26 Specialized impeller and chopper for Diosna 25. (From Ref. 22.)

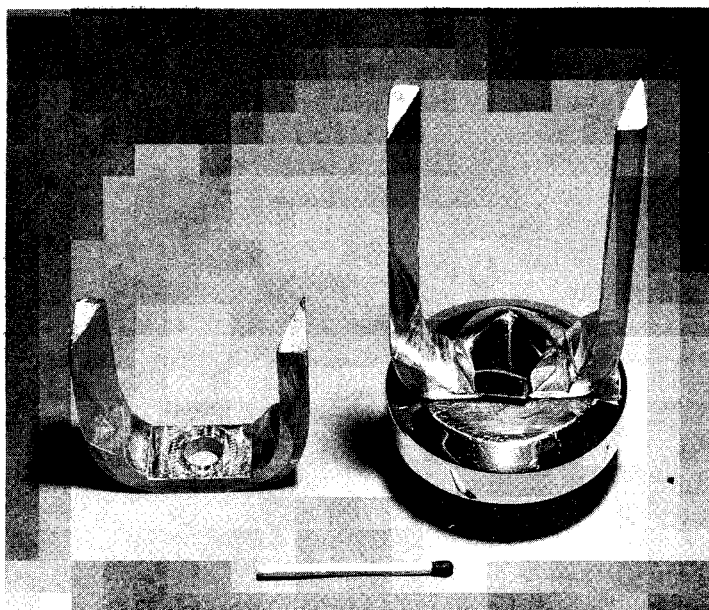


Fig. 27 Different design of choppers used in Fielder PMA 25. (From Ref. 5.)

because only part of the starting material is affected, the granulation process is difficult to control and reproduce [5].

By lining the inner wall of the bowl with polytetrafluoroethylene (PTFE) the amount of deposited material can be reduced significantly [5]. A forward inclination of the impeller blades in the direction of rotation has been claimed to result in a lower degree of adhesion of wetted material during processing and has been patented with reference to Powrex.

## VII. INSTRUMENTATION FOR ENDPOINT DETECTION

Wet granulation in high shear mixers can be a difficult unit operation to scale up and reproduce owing to lack of means for directly detecting the endpoint. A direct endpoint detection requires that the granule size distribution can be measured continuously during the process. Process control systems based on this principle are available for fluid beds, measuring the particle size by laser diffraction by inserting a product loop. However, this option is still very expensive and has not been applied to the control of granulation in high shear mixers.

Indirect monitoring of the process is possible using various sensor devices and principles. The

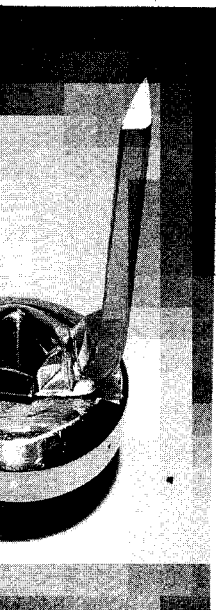
1. Measurements derived from the process
  - Conductivity [41]
  - Capacity [42]
  - Resistance [42]
  - Impact force [1]
2. Measurement derived from the motor
  - Power consumption [43]
  - Motor slip [44,45]
  - Torque [46]

The only probe method for endpoint detection is the probe [1] originally developed by Diosna mixers at Boots Company. It measures the change in momentum of granules as they pass through the mass that affects its strain rate. The probe is used to detect events (e.g., lumps caused by agglomeration). The parameters considered were power consumption, torque, and motor slip. The signal for endpoint detection is generated when the signal satisfies a certain preset value within a certain period [1].

A more convenient method for endpoint detection is based on measuring the rheological properties, such as torque on the motor shaft, power consumption, or the mechanical point of view, power consumption. Power consumption measurement on the shaft gives a direct indication of the mass against the impeller. This method is simple and expensive. The difference between the input power ( $P_i$ ), transmitted power to the motor ( $P_m$ ), and the output power ( $P_o$ ) is the power lost in the motor [28].

The differences between the input power and the output power are many factors (i.e., slip, friction, etc.). However, instrumentation based on torque measurement is enough to reflect the changes in the process. Torque is correlated with the direct torque measurement on the motors using a DC drive unit. The torque is measured on the torque, although the correction factor for AC motors, which require a torque measurement.

The slip of the motor is a measure of the motor's efficiency. It has the advantage of its sensitivity to the process.



Fielder PMA 25. (From Ref. 5.)

s affected, the granulation process

owl with polytetrafluoroethylene  
can be reduced significantly [5].  
es in the direction of rotation has  
of adhesion of wetted material  
with reference to Powrex.

## POINT DETECTION

be a difficult unit operation to  
means for directly detecting the  
quires that the granule size distri-  
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Indirect monitoring of the granulation process can be based on different devices and principles. These include the following:

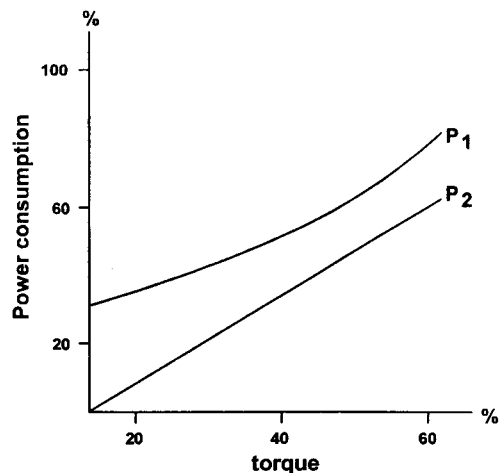
1. Measurements derived from *probes*:
  - Conductivity [41]
  - Capacity [42]
  - Resistance [42]
  - Impact force [1]
2. Measurement derived from the *impeller motor* or *impeller shaft*:
  - Power consumption [43]
  - Motor slip [44,45]
  - Torque [46]

The only probe method with practical application, so far, is the Boots' probe [1] originally developed for the control of granulation processes in Diosna mixers at Boots Company. The probe is supposed to detect the change in momentum of granules moving in a constant velocity region of the mass that affects its strain gauges. To avoid bias caused by random events (e.g., lumps caused by inhomogeneous liquid distribution), the control parameters considered were pulse heights, sample time, and pulse density of the signal. The signal for endpoint control of wet-massing time has to satisfy a certain preset value for sufficient pulses above a certain height within a certain period [1].

A more convenient method of monitoring the granulation process is based on measuring the rheological properties of the mass by means of torque on the motor shaft, power consumption, or motor slip. From a technical point of view, power consumption monitoring is the simplest. Torque measurement on the shaft gives the most accurate values of the resistance of the mass against the impeller, but transmission of the signal is complicated and expensive. The difference between power consumption of the motor ( $P_1$ ), transmitted power to the motor shaft ( $P_2$ ), and torque is shown in Fig. 28.

The differences between  $P_1$  and  $P_2$  are a result of the combination of many factors (i.e., slip, friction, or internal loss in stator and rotor) [47]. However, instrumentation by means of power consumption is sensitive enough to reflect the changes in the granulation process and is satisfactorily correlated with the direct torque measurement [46]. For DC motors (or AC motors using a DC drive unit) a current measurement adequately expresses the torque, although the correlation is not perfectly linear. This is not true for AC motors, which require measurement of the power consumption or torque.

The slip of the motor is proportional to the torque of the motor and has the advantage of its sensitivity and linearity of response over the range



**Fig. 28** Correlation between torque on motor shaft and power consumption of the motor  $P_1$  and transmitted power  $P_2$ . Arbitrary scales.

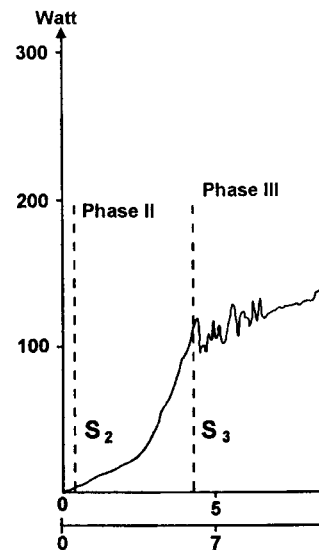
of motor load [48,49]. Motor slip is the difference between synchronous speed (no load) and operating speed (with load). Slip measurement is a relatively simple method with commercially available devices, but technical modification of the mixer might be necessary for the installation.

### VIII. ENDPOINT DETECTION

A power consumption profile is shown in Fig. 29, recorded during the granulation of lactose 200 mesh in a Diosna P10 high shear mixer [50].

The shape of the power consumption curve is claimed to be correlated with the strength of the agglomerates, assuming the granule porosity to be constant during processing [51]. The five phases of the power profile in Fig. 29, are interpreted as follows [51]:

1. *First phase:* No increase in power consumption is observed. The powder particles are moistened, the granulation liquid is adsorbed without formation of liquid bridges.
2. *Second phase:* A sharp increase in power consumption is observed. The buildup of liquid bridges between the powder particles begins and the first granules are formed.
3. *Third phase:* The power consumption levels off. The addition of granulation liquid results in a fill-up of the interparticular voids and the formation of coarser granules.



**Fig. 29** Power consumption profile recorded during the granulation of lactose 200 mesh, and deionized water as granulation liquid.

4. *Fourth phase:* Lactose granules are formed, the granules are filled with liquid, the granules are saturated. The porosity of the granules is equal to the porosity of the powder.
5. *Fifth phase:* After the granules are saturated, the granules pass into a suspension.

It has been claimed that the granulation process lies in the range of 0.5 to 1.0, normalized as given in Eq. (2):

$$\pi = \frac{S - S_2}{S_5 - S_2}$$

Where  $\pi$  is the normalized power consumption,  $S$  is the power consumption, and  $S_2$  and  $S_5$  are the power consumption at the start and end of the granulation process, respectively. The authors stated that  $\pi$  is equal to 1.0 for fully saturated granules, and that the granulation process is controlled by the agglomeration properties of the powder. The saturation is a controlling factor in the granulation process, and the ground for this assumption



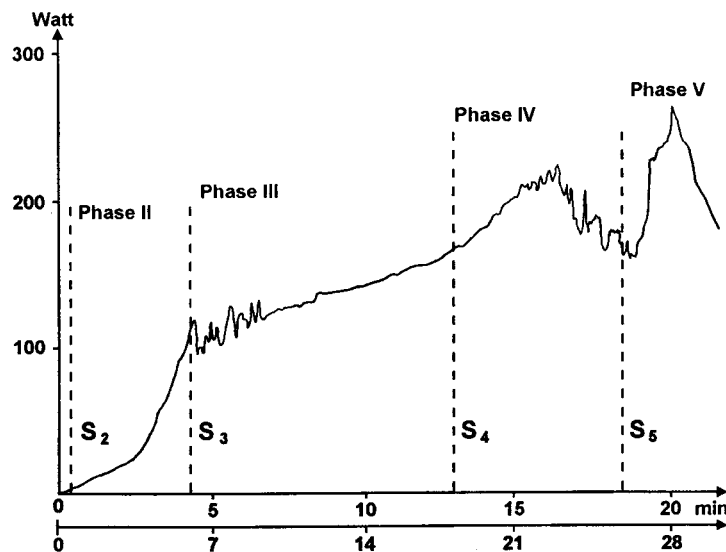


Fig. 29 Power consumption profile (Diosna P10 high-shear mixer, lactose 200 mesh, and deionized water as binder liquid added at constant rate). (From Ref. 50.)

4. *Fourth phase:* Large areas in the particulate system are completely filled with liquid that leads to buildup of comparatively coarse granules. The power consumption rises for a while. The liquid saturation is equal to 100% at point  $S_5$ .
5. *Fifth phase:* After an increase in power consumption the system passes into a suspension.

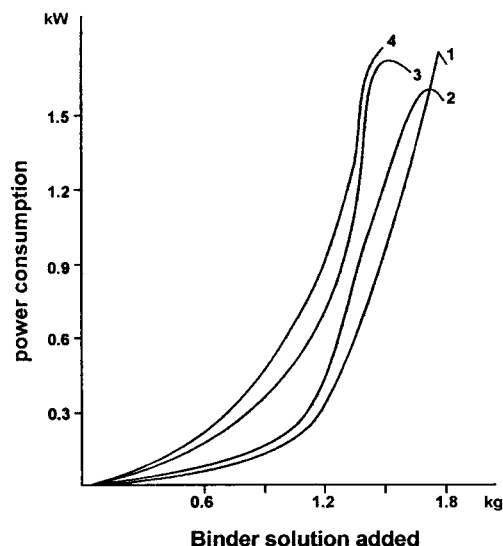
It has been claimed that the amount of liquid required to run a robust process lies in the range of  $S_3$ – $S_4$  [49]. The amount of liquid can be normalized as given in Eq. (2) [50]:

$$\pi = \frac{S - S_2}{S_5 - S_2} \quad (2)$$

Where  $\pi$  is the normalized liquid quantity,  $S$  is the absolute liquid quantity and  $S_2$  and  $S_5$  are the parameters of the power consumption profile. The authors stated that  $\pi$  is equivalent to the liquid saturation of the moist agglomerates, and that the use of  $\pi$  enables a direct comparison of the agglomeration properties of different starting materials. Because the liquid saturation is a controlling factor for granule growth, there is rational background for this assumption.

The shape of the power consumption profiles shown in Fig. 29 is recognized for other types of formulations [43] relative to the three first phases. These compositions generally comprise lactose in mixture with starch. However, the identification of the second or third phase can be compromised at low impeller speed and high liquid addition rate [26,52] when granulating lactose. The change of binder from PVP to HPMC added dry, compromises the detection of the third phase, when granulating a formulation containing lactose and starch [43]. This effect was explained by the retarded dissolution of HPMC in the liquid binder (water). If the agglomerates are heavily densified during liquid addition (i.e., dicalcium phosphate), the suggested characteristic phases of the power consumption curve disappear (Fig. 30). The energy consumption rises steeply because of the compaction of the agglomerates and the high granule growth rate within narrow moisture limits [26].

The energy consumption by wet granulation (i.e., the cumulative power consumption) is converted completely into heating the mixer and its contents [53]. The absorption of the kinetic energy of the particles results in heat. When



**Fig. 30** Power consumption profile during liquid addition: material, dicalcium phosphate; liquid binder, 15% aqueous solution of Kollidon VA64; 1 and 2, impeller speed 250 rpm; 3 and 4, impeller speed 500 rpm; 2 and 3, spray rate 100 g/min; 1 and 4, spray rate 300 g/min; chopper speed, 3000 rpm; high shear mixer: Fielder PMAT 25. (From Ref. 26.)

growth by coalescence of agglomerates is limited by agglomerate deformability. Therefore, there is a fundamental relationship between the power consumption profile and granule growth rate. Granule growth rate is limited by agglomerate deformability. The correlation between granule growth rate and power consumption has been demonstrated. This was verified, by granulating a formulation containing lactose and starch that the level of power consumption was correlated with the level of mobile liquid bondings in the agglomerates. The bondings are correlated with the surface tension of the liquid binder.

On the basis of the foregoing, a control strategy for a specific granulation process can be developed. The control strategy is based on the reflection of the impeller motor reflected power consumption and the ability of the granules to grow. The power consumption profile is a function of the variables (i.e., densification, granule growth rate, etc.). The control strategy for a specific granulation process is based on the reflection of the impeller motor reflected power consumption and the ability of the granules to grow. Also, some practical considerations are:

1. The liquid binder must be added at a rate to avoid local saturation.
2. The liquid binder must be added at a rate to avoid local saturation.
3. Buildup of stationary agglomerates in the bowl during liquid addition.
4. The binder must be added at a rate to avoid local saturation. Alternatively, a control strategy for a specific granulation process is based on the reflection of the impeller motor reflected power consumption and the ability of the granules to grow.

Nonhomogeneous liquid distribution is a problem in granulation. If a part of the volume is not wetted, the load signal is unreliable. The control strategy for a specific granulation process is based on the reflection of the impeller motor reflected power consumption and the ability of the granules to grow. The control strategy for a specific granulation process is based on the reflection of the impeller motor reflected power consumption and the ability of the granules to grow. The control strategy for a specific granulation process is based on the reflection of the impeller motor reflected power consumption and the ability of the granules to grow.

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the particles results in heat. When

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000 rpm; high shear mixer: Fielder

growth by coalescence of agglomerates becomes significant, because of high agglomerate deformability the energy consumption will increase accordingly. Therefore, there is a fundamental correlation between the power consumption profile and granule growth because both are influenced by the agglomerate deformability. The correlation between power consumption and granule growth has been demonstrated in several publications [26,33,43,53,54]. It was verified, by granulating dicalcium phosphate with various binders [54], that the level of power consumption is correlated with the strength of the mobile liquid bondings in the moist agglomerates. The strength of these bondings are correlated with the porosity function  $(1 - \epsilon)/\epsilon$  of the agglomerates and the surface tension of the binder solution [34].

On the basis of the foregoing survey, it can be concluded that the load of the impeller motor reflects changes during granulation related to granule growth and the ability of the mass to absorb mixing energy. The shape of the power consumption profile during granulation is influenced by product variables (i.e., densification properties and binder type) and the process variables (i.e., impeller speed and liquid addition rate). Hence, the process control strategy for a specific composition must be based on practical experiences. Also, some practical factors should be noted when using load controllers:

1. The liquid binder must be added continuously at a slow-pumping rate to avoid local overwetting.
2. The liquid binder should be distributed by a spray nozzle to assure homogeneous liquid distribution.
3. Buildup of stationary material on the impeller or the wall of the bowl during liquid addition should be prevented.
4. The binder must be added as a dry powder to maintain the composition; thus, the optimal method would be to add it in solution. Alternatively, a concentrated binder solution could be added preliminary to the solvent.

Nonhomogeneous liquid distribution causes fluctuations in the load signal [52]. If a part of the wetted mass is deposited on the wall of the bowl, the load signal is unreliable. An automatically controlled granulation process starts with a timer-controlled dry blending of the feed materials [43]. After blending, a peristaltic pump is activated and the granulating liquid is distributed through a spray nozzle. The process is now exclusively controlled by the power consumption signal. The power consumption increases, and if the specific phases shown in Fig. 29 are present,  $S_3$  can be identified as a peak signal in the first derivative of the power consumption signal. Depending on the granule size requirement of the product, the liquid addition continues after the peak signal for a predetermined period. After the pump

is turned off, the wet massing proceeds for a specified time, or is stopped at a preselected level of power consumption.

If the typical phases in the power consumption profile are absent, an alternative to the peak detection mode is to stop the liquid addition at a predetermined level of power consumption, continued by a timer- or power level-controlled wet-massing phase. The sequence of controlling wet-massing time, agitator speeds, liquid addition time, and liquid flow rate can be PLC-based and retrofitted or installed in new high shear mixers.

Several publications [43–45,55] have proved that measurement of power consumption and process monitoring can improve the product quality. The following advantages are obtained:

- Automation of the wet agglomeration process
- Keeping the product within predefined quality limits
- Optimizing the amount of granulating liquid irrespectively of minor variation in properties of feed materials
- Documentation of the adherence to the described manufacturing procedures.

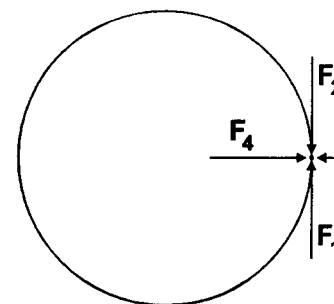
## IX. PROCESS SCALE-UP

Scale-up of wet granulation processes from laboratory scale to pilot and production scale is problematic. Even within the same manufacture and type of mixer, liquid requirement and granule properties in terms of granule size distribution and granule porosity might change significantly by scaling-up [21,22]. Besides, the impact on the mass cannot be kept constant in a scale-up operation owing to inevitable changes in impact forces. For reasons of simplification we will consider the particles to be under impact of four forces acting on each particle at the periphery of the bowl, excluding gravity (Fig. 31):

1. Acceleration force  $F_1$  (impact of impeller)
2. Frictional force  $F_2$
3. Centripetal force  $F_3$
4. Centrifugal force  $F_4$

The centrifugal force is simply wiping the particles against the wall of the bowl and centripetal force is the reaction force of the wall. In other words, the centrifugal and centripetal force create a zone of compaction. The centrifugal force  $F_c$  is given by Eq. (3):

$$F_c = \frac{mv^2}{r} = ma_c \quad (3)$$



**Fig. 31** The forces acting on a particle at the periphery of the bowl:  $F_1$ , impact force of impeller;  $F_4$ , centrifugal force.

where  $m$  is the mass of the particle,  $v$  is the velocity of the bowl and  $a_c$  is the centrifugal acceleration. The impact force of the particles is lower than the tip speed of the impeller. A comparison of the centrifugal forces in different mixers as demonstrated in Table 3.

The data on centrifugal forces show that the higher compaction forces in the high shear mixers. Furthermore, one must consider the acceleration forces, exerted on the particles during downscaling, potentiating the

**Table 3** Comparison of Impeller Speed and Acceleration at the Two Fixed Impeller Speeds 10–1800 L

	PMA 10	PM 20
Bowl diameter (m)	0.30	0.4
Impeller speed (rpm) I/II	278/556	278/556
Tip speed ( $m \cdot s^{-1}$ ) I/II	4.3/8.6	5.9/11.8
Centrifugal acceleration ( $m \cdot s^{-2}$ ) I/II	124/496	171/684

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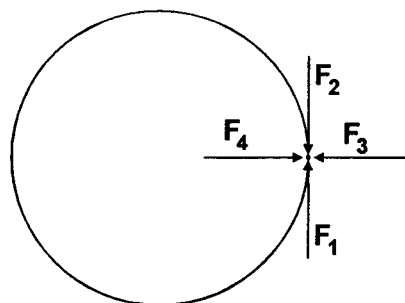
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**Fig. 31** The forces acting on particles at the wall of the bowl by impact of an impeller:  $F_1$ , impact force of impeller;  $F_2$ , frictional force;  $F_3$ , centripetal force;  $F_4$ , centrifugal force.

where  $m$  is the mass of the particle,  $v$  is the velocity of particles,  $r$  the radius of the bowl and  $a_c$  is the centrifugal acceleration. The velocity of the particles is lower than the tip speed; however, it can be used as a basis for a comparison of the centrifugal acceleration for different scales of high shear mixers as demonstrated in Table 3.

The data on centrifugal acceleration reveal that one might expect higher compaction forces in smaller machines at the same level of tip speed. Furthermore, one must consider that the frictional forces and, hence, the acceleration forces, exerted by the impeller, are likely to be increased by downscaling, potentiating the impact on the agglomerates. On the contrary,

**Table 3** Comparison of Impeller Speed, Tip Speed of Impeller, and Centrifugal Acceleration at the Two Fixed Impeller Speeds I/II of Fielder PMA High Shear Mixers 10–1800 L

	PMA 10	PMA 25	PMA 65	PMA 150	PMA 300	PMA 800	PMA 1800
Bowl diameter (m)	0.30	0.41	0.51	0.75	0.94	1.31	1.73
Impeller speed (rpm) I/II	278/556	278/556	218/436	135/270	108/216	78/156	59/118
Tip speed ( $m \cdot s^{-1}$ ) I/II	4.3/8.6	5.9/11.9	5.7/11.4	5.2/10.4	5.3/10.6	5.3/10.6	5.3/10.6
Centrifugal acceleration ( $m \cdot s^{-2}$ ) I/II	124/496	171/694	128/514	72/290	60/329	43/172	32/130

if the centrifugal forces are kept constant by decreasing the tip speed in the smaller mixers, the toroidal flow pattern of the mass will be compromised. It is likely that the design of the impeller can partly compensate for the difference in impact forces. In one study [56], agitator designs in different scale of Diosna mixers were compared on the basis of their relative swept volume (see Sec. VI). The relative swept volume is related to the energy input efficiency of the agitator. The relative swept volume of both chopper and impeller was highly reduced when the volume of the bowl was increased from 25 to 600 L. It had the practical implication that a significantly prolonged wet-massing time was necessary when scaling-up. To improve the scale-up of granulation processes in a Diosna, both chopper and impeller designs were modified in Diosna 25 to obtain a lower swept volume. This strategy resulted in similar wet-massing times to obtain a specific granule size in 25- and 600-L scale.

In a comparison of different scales of high shear mixers [21,22], the variations in growth rates obtained in the mixer could be attributed to a different intensity of agitation, as expressed by the swept volume. The comparison was based on wet granulation of dicalcium phosphate, which undergoes densification during processing. Accordingly, a higher relative swept volume resulted in a greater increase of the product temperature and in denser granules. Table 4 shows a comparison of relative swept volume of the impeller of Fielder and Diosna mixers of different scales [57].

There is only a slight decrease in relative swept volume when scaling-up in Fielder mixers. In laboratory and pilot scales the relative swept volume is higher in Diosna mixers than Fielder mixers. Accordingly, the Diosna

**Table 4** The Relative Volume Swept Out by the Impeller in PMA and Diosna Mixers of Different Scale

Type of mixer	Relative swept volume per second at low/high speed
Diosna P25	1.37/2.74
Diosna P50	1.08/2.16
Diosna P250	0.52/1.03
Diosna P400	0.36/0.72
Fielder PMAT 25	0.75/1.51
Fielder PMAT 65	0.71/1.42
Fielder PMAT 150	0.61/1.23

Source: Ref. 57.

mixers produced denser granules than Fielder mixers [22]. Where the swept volume is constant, the difference between Diosna P250 and Fielder PMA series high shear mixers in a study in Fielder PMA series high shear mixers characteristics of the final products should be considered: (a) The rotation speed to be kept constant. (b) The scale-up based on batchsize. (c) The scale-up based on a ratio of impeller speed.

Direct scaling-up of the agitator design to a larger scale is based on the relative amount on different scales of granulation, moisture content in the mass. The power input in high shear mixers is high that is pronounced in the smaller scales of granulation. Surprisingly, this means that a liquid binder was required in the smaller scale-up, the reduced evaporation of liquid intragranular porosity so that the granule size is constant.

Identification of scale-up of granulation model [59]. The model is applicable for the determination of the viscosity of the granule. The power number defined by the Reynold number defines the technique depends on the fact that the intensity of mixing, the rotation speed, and Reynold number will be independent of the scale. The optimal wet mass can be calculated in a small scale and the optimal wet mass can be calculated.

A proposal for scaling-up of granulation compares granulation of lactose in a pilot scale type (10, 75, and 300 L). The granule size increase and granule size could be kept constant. The dimensionless number  $N$  where  $N$  is the rotation speed and  $g$  is the gravitation constant. The relative centrifugal acceleration to the gravitation is a constant swept volume nor a constant process. An equal Froth number times in achieving similar granule size.

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mixers produced denser granules of dicalcium phosphate than did the Fielder mixers [22]. Where the swept volume was similar, no significant differences between Diosna P250 and Fielder PMAT were observed. In a scaling-up study in Fielder PMA series high shear mixers that compared granule characteristics of the final products [58], it was concluded that three important factors should be considered: (a) The impeller tip speed (radial velocity) has to be kept constant. (b) The amount of binder liquid should be linearly scaled-up based on batchsize. (c) The wet massing time should be adjusted based on a ratio of impeller speeds from one scale to the next.

Direct scaling-up of the amount of binder solution by adding the same relative amount on different scales does not necessarily lead to a constant moisture content in the mass. The marked heat production, caused by the high power input in high shear mixers, results in the evaporation of water that is pronounced in the small mixers because of the more intensive agitation. Surprisingly, this means that approximately the same amount of liquid binder was required in small- and large-scale mixers [21]. When scaled-up, the reduced evaporation of water compensated for the higher intragranular porosity so that the liquid saturation level was kept almost constant.

Identification of scale-up parameters might be based on a rheological model [59]. The model is applied from the mixing of liquid and requires the determination of the viscosity of the wet mass by mixer torque rheometry. The power number defines the basic flow pattern within the mixer, and the Reynold number defines the viscous forces of the mass. The proposed technique depends on the fact that for mixers of similar geometry and rates and intensity of mixing, the relation between the power number and the Reynold number will be independent of the scale of the mixer. If this relation can be established in a small mixer, and the point on the curve relevant to the optimal wet mass can be identified, the settings of the larger mixer can be calculated.

A proposal for scaling-up parameters has been published [60] that compares granulation of lactose in three high shear mixers of the Collete-Gral type (10, 75, and 300 L). The granulation process relative to temperature increase and granule size could be scaled up by keeping the Froude number constant. The dimensionless Froude number expresses the value of  $N^2D/g$ , where  $N$  is the rotation speed in rpm,  $D$  is the diameter of the impeller, and  $g$  is the gravitation constant. The Froude number is the ratio of the centrifugal acceleration to the gravitation constant. It was concluded that neither a constant swept volume nor constant impeller tip speed resulted in a comparable process. An equal Froude number resulted in comparable processing times in achieving similar granule size distributions.

A more practical approach to the scale-up is based on monitoring the power consumption profile of the impeller motor [50] using the peak detection mode as control parameter of the liquid requirement (see Sec. VIII).

It is unlikely that a single parameter, such as swept volume, energy input, centrifugal force, or tip speed, is applicable as a controlling factor of scaling-up the process parameters. Because of the fundamental physical laws, higher impact is obtained in small-scale high shear mixers compared with larger scale at equal impeller tip speed. It means more densified granules are to be expected in laboratory-scale and pilot-scale mixers than in production scale for those agglomerates that can withstand the degradation forces. In contrast, the higher degradation forces applied in the laboratory-scale mixers might comminute agglomerates of lower strength, resulting in a wider granule size distribution and irregular granule shape than found with larger mixers. This was demonstrated in a study applying the optimal scale-up conditions for a 10-L on a 50-L Roto mixer when granulating lactose in mixture with corn starch [38].

It is obvious that the scaling-up strategy is dependent on the formulation to be granulated and must be based on trials with the specific composition, or with a placebo composition with similar granulation characteristics. It seems rational that the energy input in the wet-massing phase should be adjusted to meet the requirement of the specific formulation when scaling-up. This requires measurement of the load of the impeller motor and the ability to adjust the impeller speed. However, because the design of agitators is arbitrary, it is often difficult to compensate for the differences in impact, dependent on the scale of mixer. The liquid requirement when scaling-up is unpredictable, because the evaporation during processing can be considerable and is dependent on product temperature and airflow through the bowl. Therefore, it is recommended that the scale-up of liquid requirement be accomplished by compensating for the loss of moisture during liquid addition with the specific high shear mixer. The variation in moisture content of the feed materials must also be considered.

## X. MELT GRANULATION

Melt granulation, or thermoplastic granulation, is based on agglomeration by use of a binder material that is solid at room temperature and softens and melts at higher temperature (i.e., 50–90°C). When melted, the action of the binder liquid is similar to that of a wet-granulation process.

The water-soluble binders used for melt granulations are polyethylene glycols (PEG) [61–63]. Solid dispersions can be prepared by dissolving a drug in the molten PEG binder [64,65]. By selecting a binder that is insol-

uble in water, melt granulation can be performed in water-soluble binders [66–68]. The binder material at ambient temperature is solid, and the melting point of the binder, the temperature of the mixture, and the heat of friction caused by agitation are important factors.

The advantages of the process are as follows:

1. The amount of liquid is easily controlled in highly reproducible batches.
2. The liquid addition is independent of the granule size.
3. For water-sensitive materials, the use of organic solvents is possible.
4. The production is continuous.

The disadvantages are:

1. The risk of chemical reactions between the product and the liquid.
2. The granules may be too soft.
3. The only water-soluble binders are of the polyethylene glycol type.

High shear mixers are used for melt granulation to their agitation energy is high enough to raise the product temperature within a short time. It is important to compare the correlation between the product temperature and the speed in different laboratories.

The Pellmix 10 (Pellmix 10, Pharmacia) of 50 L and is specified for melt granulation. The mixer possesses the necessary heating within a short process time to reach a product temperature of 60–70°C. The heating phase can be shortened by preheating the mixer. The Pellmix 10 mixer is also capable of producing granules in a 10, 60, and 600 L scale. The heat of friction was possible to be controlled by agitation can be compensated by preheating.

The main factors influencing the process are the binder and its viscosity, the heating to the melting point, the heat of friction, the viscosity, the effects of the product on the binder, and the heat of wet granulation.



re-up is based on monitoring the motor [50] using the peak detection requirement (see Sec. VIII).

such as swept volume, energy applicable as a controlling factor of use of the fundamental physical scale high shear mixers compared to low shear mixers. It means more densified granules and pilot-scale mixers than in laboratory-scale mixers that can withstand the degradation forces applied in the laboratory-mixers of lower strength, resulting in more uniform granule shape than found with the laboratory mixers. In this study applying the optimal scale-mixer when granulating lactose in

ogy is dependent on the formulation trials with the specific compound. Similar granulation characteristics in the wet-massing phase should be achieved for a specific formulation when scaling-up. The design of the impeller motor and the agitator, because the design of agitators is different, can account for the differences in impact, mixing, and liquid requirement when scaling-up is required. The wet-massing processing can be considered as a function of air and airflow through the bowl. The scaling-up of liquid requirement based on the amount of moisture during liquid addition and the variation in moisture content of the granules.

ion, is based on agglomeration at room temperature and softens at 100°C). When melted, the action of the granulation process.

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uble in water, melt granulation is a way of producing sustained-release granules [66–68]. The binder is added either in powder form to the starting material at ambient temperature [63–67], followed by heating above the melting point of the binder, or in molten form to the heated materials [64,66]. The temperature of the mixture is increased by a heating jacket [6] and by heat of friction caused by agitation [66,77].

The advantages of this process compared with wet granulation are as follows:

1. The amount of liquid binder can be controlled precisely, resulting in highly reproducible granule properties.
2. The liquid addition and drying phases are eliminated.
3. For water-sensitive materials, melt granulation is an alternative to the use of organic solvents.
4. The production labor and equipment costs are reduced.

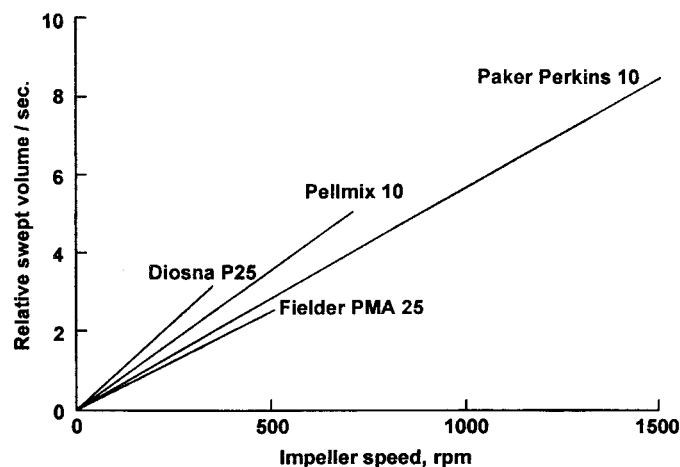
**The disadvantages are**

1. The risk of chemical degradation of thermolabile substances (i.e., loss of water of crystallization).
2. The granules must be cooled before further handling.
3. The only water-soluble melt binders for immediate release granules are of the polyethylene glycol type.

High shear mixers are advantageous to use for melt granulation owing to their agitation energy input that is sufficient to generate the required product temperature within an acceptable processing time. Figure 32 compares the correlation between relative swept volume and impeller rotation speed in different laboratory-scale mixers.

The Pellmix 10 (Pelletprocessor, PP10-prototype) has a bowl volume of 50 L and is specified for melt granulation and melt pelletization. This mixer possesses the necessary energy input to ensure melting by frictional heating within a short processing time (i.e., approximately 10 min to reach a product temperature of 60°C at 600 rpm). By external heating of the bowl, the heating phase can be shortened to about 5 min. The Baker Perkins 10 mixer is also capable of providing a high-energy input. Three scales of this mixer (10, 60, and 600 L) have been examined, and melt granulation by heat of friction was possible in all of them [67]. The limited energy input by agitation can be compensated by external heating of the jacket [62].

The main factors influencing agglomeration are the relative amount of binder and its viscosity, the impeller rotation speed, and massing time after heating to the melting point [5,64,69]. Except for an effect of binder liquid viscosity, the effects of the other factors mentioned, agree well with results of wet granulation.



**Fig. 32** Correlation between relative swept volume and impeller rotation speed in laboratory-scale high shear mixers. (From Ref. 69.)

The granule growth of dicalcium phosphate can be correlated with the liquid saturation of the agglomerates. Rapid growth by the coalescence mechanism was seen at 80–85% saturation of melt binder [63]. Granules prepared by melt granulation with PEG contain the solidified binder and, therefore, are less porous than wet granulated granules. The optimum amount of binder to agglomerate the particular dicalcium phosphate was in the range of 37–43% v/v at melt granulation and slightly higher by wet granulation [63].

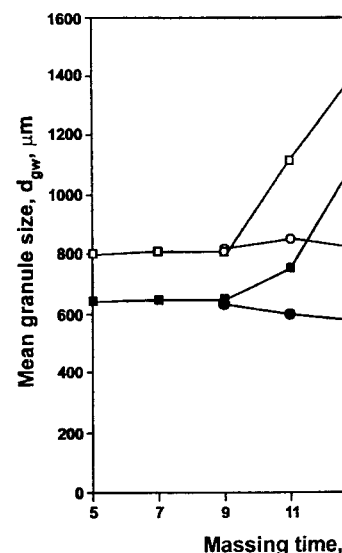
The results obtained with lactose were different. Agglomerates of lactose were consolidated to their minimum porosity after a short massing time [63]. In wet granulation the granule size remains unchanged during wet massing. In contrast, melt granulation of lactose showed a constant growth with massing time, despite constant saturation with the liquid binder. It is assumed that the high viscosity of the binders (PEG 3000 and PEG 6000) contributes significantly to the strength of the lactose agglomerates. In comparison with wet granulation, the agglomerates are not degraded, and granule growth proceeds during the massing phase.

The amount of binder necessary for wet granulation (10–15% v/v) was considerably lower than that required for melt granulation (21.2–25.4% v/v) for a similar lactose quality. The liquid requirement is dependent on the particle size of lactose, being increased with reduced particle size [70]. The range of liquid saturation required to produce growth by

coalescence by melt granulation was obtained for dicalcium phosphate. The granulation of lactose is produced by liquid binder.

Figure 33 shows the granule growth in a high shear mixer. The high shear mixer speed [62,64,69]. Except for the granule growth, PEG 3000 produces granules means that the less viscous liquid binder means lower viscosity of the melted binder, lower product temperatures, less agglomeration. Because the viscosity of PEG 3000, this effect is most pronounced.

The effect of binder viscosity on the agitation intensity, heating, granule structure, and the amount of binder known to influence the granule growth.



**Fig. 33** Effects of type of polyethylene glycol binder concentration and impeller speed, 500 rpm (●, ○) Pelletprocessor, PP10. (From Ref. 69.)

ker Perkins 10

1500

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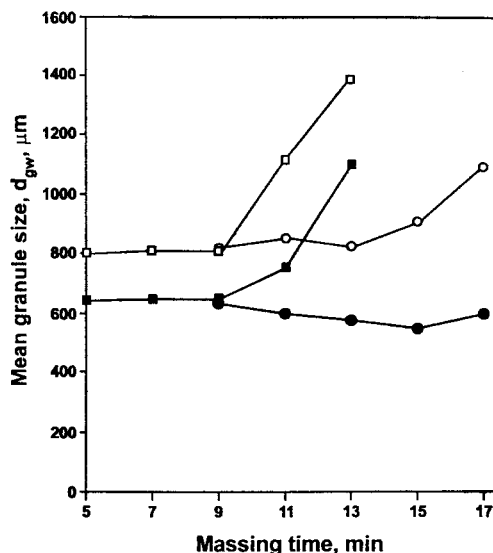
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size required to produce growth by

coalescence by melt granulation was 80–90%, comparable with the values  
obtained for dicalcium phosphate. The lower liquid requirement for wet  
granulation of lactose is probably due to the solubility of lactose in the  
liquid binder.

Figure 33 shows the granule growth of lactose by melt granulation in  
a high shear mixer. The highest granule size is obtained at high impeller  
speed [62,64,69]. Except for the effect of impeller rotational speed on gran-  
ule growth, PEG 3000 produces larger granules than with PEG 6000. This  
means that the less viscous liquid binder produces the largest granules. The  
viscosity of the melted binder can be critical to the granulation process at  
lower product temperatures, leading to formation of lumps by uncontrolled  
agglomeration. Because the viscosity is higher for PEG 6000 than with PEG  
3000, this effect is most pronounced for PEG 6000 [71].

The effect of binder viscosity on pelletization might be dependent on  
the agitation intensity, heating method used, the particle size and surface  
structure, and the amount of binder [72]. The particle size of the binder is  
known to influence the granule size [62]. When comparing a fine, coarse,



**Fig. 33** Effects of type of polyethylene glycol and impeller speed on mean granule size during massing: binder concentration, 23% PEG 3000 (○, □); PEG 6000 (●, ■); impeller speed, 500 rpm (●, ○); 700 rpm (□, ■); high shear mixer: Prototype of Pelletprocessor, PP10. (From Ref. 69.)

and flake quality of PEG 6000, the amount of oversize fraction in the product was lowest for the fine quality and highest for the flake quality. The effect disappears with the prolonged massing [62] required for pelletization. The granule size distribution is affected by impeller speed [64,69], producing a narrower size distribution at a high impeller speed. Pellets can be produced at high impeller speed and extended massing time [69]. By incorporating lipophilic melt binders, such as glyceryl monostearate and wax, matrix pellets for prolonged-release products can be obtained [70].

The cooling procedure of the granulate must be considered. The most convenient method of cooling the product is to apply cooling water to the jacket and allow the product to cool down to a temperature (i.e., 10°C below melting point of the binder at low-speed agitation) [61,62,67]. The bulk density of the product is reduced during this procedure, whereas by cooling in a fluid bed the product properties remain unaffected [62,73]. The cooling period in production-scale high shear mixers can be a time-consuming process owing to the limited ratio of cooling transfer surface area to mixer load. The cooling process can be shortened by introduction of air through the product by an immersion sword or air-stripping system [73].

Sieving of the product is necessary to reduce the number of lumps [64]. The product is normally sieved after the cooling procedure. If the sieved product is cooled on trays, the product must be sieved again because granules will be sintering. For the production of immediate-release granules, only PEG is suitable as a binder unless the active substance is highly soluble. PEG 6000 should be preferred because, contrary to PEG 3000, it is non-hygroscopic at normal humidities and temperatures. Incompatibility between PEG and other ingredients in the formulation must be considered, for PEG can be oxidized or react through its hydroxyl groups. Addition of antioxidants such as  $\alpha$ -tocopherol might stabilize the formulation [73]. It is recommended that excipients with water of crystallization be avoided and that the active substance is ensured to be thermostable up to 100°C. A jacketed high shear mixer with sufficiently high agitation energy input should be applied for processing, setting a jacket temperature (i.e., 15°C) over the melting point of the binder.

A massing phase of 3–15 min normally results in a satisfactory granule quality for further processing. Lubricants and disintegrants are mixed with the granules to achieve satisfactory tableting properties [61].

The method of melt granulation in high shear mixers has a great potential, because both immediate-release granules as well as pellets for coating or matrix pellets can be produced in one simple process. Therefore, it is surprising that this technique is not more widespread in production, considering that the scaling-up problems are limited.

## XI. SUPPLIERS LIST

1. Fielder PMA, Spectrum, Aeromatic-Fielder Ltd.  
Mayflower Close  
Eastleigh, Hampshire SO5  
Tel. 1703267131 Fax 170  
Niro Inc., Aeromatic-Fielder  
9165 Rumsey Road, Columbus, OH  
Tel. (410)997-7010 Fax (410)997-7011  
Types: Vertical high shear mixer, chopper  
Specialized high shear mixer, chopper  
Options: Vacuum, special controller device
2. Bohle  
L.B. Bohle, Maschinen & Apparatebau  
Postfach 1162, D-59303  
Tel. 0254/5072 Fax 0254/5073  
Type: Vertical high shear mixer  
Options: Vacuum, special controller device
3. Gral  
Machines Colette N.V.  
Keerbaan 70  
B-2160 Wommelgem, Belgium  
Tel. 03/3501211 Fax 03/3501212  
Type: Vertical high shear mixer  
Options: Vacuum, special controller device
4. Diosna  
Dierks & Söhne GmbH  
P.O. Box 1980 Sandbach  
D-4500 Osnabrück, Germany  
Tel. (0541)33104-0 Fax (0541)33104-1  
Type: Vertical high shear mixer  
Options: Vacuum, jacketed bowl
5. Lödige  
Gebrüder Lödige Maschinenbau  
Postfach 2050, D-33050, Bielefeld  
Tel. (05251)309-0. Fax (05251)309-1  
Types: Horizontal and vertical high shear mixers  
Options: Jacketed bowl

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t for the flake quality. The effect  
2] required for pelletization. The  
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one simple process. Therefore, it  
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## XI. SUPPLIERS LIST

1. Fielder PMA, Spectrum, Pelletprocessor (PP)  
Aeromatic-Fielder Ltd.  
Mayflower Close  
Eastleigh, Hampshire S053AR, UK.  
Tel. 1703267131 Fax 1703253381  
Niro Inc., Aeromatic-Fielder Division  
9165 Rumsey Road, Columbia, MD 21045, USA  
Tel. (410)997-7010 Fax (410)997-5021  
Types: Vertical high shear mixers with side-mounted chopper  
Specialized high shear mixer for melt and wet pelletization without  
chopper  
Options: Vacuum, special gas inlet, microwaves, jacketed bowl, process  
controller device
2. Bohle  
L.B. Bohle, Maschinen & Verfahren GmbH  
Postfach 1162, D-59303 Ennigerloh, Germany  
Tel. 0254/5072 Fax 0254/4429  
Type: Vertical high shear mixer with changeable bowl  
Options: Vacuum, special gas inlet, microwaves, jacketed bowl
3. Gral  
Machines Colette N.V.  
Keerbaan 70  
B-2160 Wommelgem, Belgium  
Tel. 03/3501211 Fax 03/3532055  
Type: Vertical high shear mixer with changeable bowl  
Options: Vacuum, microwaves, jacketed bowl, process controller  
device
4. Diosna  
Dierks & Söhne GmbH  
P.O. Box 1980 Sandbachstrasse 1  
D-4500 Osnabrück, Germany  
Tel. (0541)33104-0 Fax (0541)33104-10  
Type: Vertical high shear mixer with side-mounted chopper  
Options: Vacuum, jacketed bowl, process controller
5. Lödige  
Gebrüder Lödige Maschinenbau-GmbH.  
Postfach 2050, D-33050, Paderhorn, Germany  
Tel. (05251)309-0. Fax (05251)309-123  
Types: Horizontal and vertical high shear mixers  
Options: Jacketed bowl

6. Moritz  
Moritz Product division  
Company PIERRE GUERIN  
Grande Rue 179  
79210 Mauze sur le Mignon, France  
Tel. 49263058 Fax 49263484  
Type: Vertical high shear mixer with top-mounted chopper  
Options: Vacuum, microwaves, jacketed bowl
7. Processall  
Processall Inc.  
10596 Springfield Pike, Cincinnati OH 45215  
Tel. (513)771-2266 Fax (513)771-6767  
Types: Horizontal and vertical high shear mixers  
Options: vertical mixer without chopper; drying by introducing hot air through the product; horizontal mixer with vacuum, jacketed bowl
8. Roto  
Zanchetta & C.  
Via della Cortee 24  
55010 S. Salvatore (Lucca), Italy  
Tel. 5832171 Fax 583217317  
Types: Vertical high shear mixer with top-mounted chopper; 10-L high shear mixer with side-mounted chopper  
Options: Vacuum, infrared drying, special gas inlet, jacketed bowl, tilting bowl; device for process control
9. Powrex (Japan), licenced by Glatt GmbH  
(Glatt VG-Vertical granulator)  
Glatt GmbH, Process Technology  
Bühlmühle  
D-79589 Binzen/Germany  
Tel. 76216640 Fax 762164723  
Types: Vertical high shear mixer with side-mounted chopper  
Options: Vacuum, special gas inlet, jacketed bowl; device for process control

## REFERENCES

1. PC Record. Practical experience with high-speed pharmaceutical mixer/granulators. *Manuf Chem Aerosol News* Nov:65, 1979.
2. PC Record. A review of pharmaceutical granulation technology. *J Powder Bulk Solids Technol* 4:33, 1980.
3. I Smart. Single pot process for granulation. *Pharm Eng M*
4. P Holm, T Schaefer, HG I in a high-shear mixer. *ST*
5. P Holm. Effect of impeller mixer. *Drug Dev Ind Pha*
6. T Schaefer, B Taagegaard a high shear mixer. *V. E* 1993.
7. HG Kristensen. Particle a eds. *Advances in Pharm* p. 221.
8. HG Kristensen, P Holm, erates in relation to granu
9. J Vertommen, A Michoel rine HCl pellets in a high 32, 1994.
10. P Holm, O Jungersen, T mixers. Part 1: Effects o 806, 1983.
11. HG Kristensen, P Holm, mixers. Part 4: Effect of I 763, 1984.
12. P Holm, O Jungersen, T mixers. Part 2: Effects of 1984.
13. A Jaegerskou, P Holm, T mixers. Part 3: Effects of Ind 46:310, 1984.
14. A Nagykalldi, L Gyarmat Mischer V25. *Pharm Ind*
15. D Vojnovic, P Selenati, F scale high shear mixer. *D*
16. N-O Lindberg, C Jönsson in a high-speed mixer, *D*
17. J Yliruusi, R Tihtonen. H parameters of granulation ules. *Acta Pharm Fen* 98
18. T Schaefer, P Holm, HG shear mixer. *Pharm Ind* 5
19. N-O Lindberg, E Hansson lation in a high-speed mi and liquid saturation. *Dru*
20. N-O Lindberg, C Jönsson high-speed mixer, *Diosna*

3. I Smart. Single pot processing and its integration within an automated production plant. *Pharm Eng* May/June:76, 1993.
4. P Holm, T Schaefer, HG Kristensen. Pelletization by controlled wet granulation in a high-shear mixer. *STP Pharm Sci* 3:286, 1993.
5. P Holm. Effect of impeller and chopper design on granulation in a high speed mixer. *Drug Dev Ind Pharm* 13:1675, 1987.
6. T Schaefer, B Taagegaard, LJ Thomsen, HG Kristensen. Melt pelletization in a high shear mixer. V. Effects of apparatus variables. *Eur J Pharm Sci* 1:133, 1993.
7. HG Kristensen. Particle agglomeration. In: D Ganderton, T Jones, J McGinity, eds. *Advances in Pharmaceutical Sciences*. London: Academic Press, 1995, p. 221.
8. HG Kristensen, P Holm, T Schaefer. Mechanical properties of moist agglomerates in relation to granulation mechanisms. *Powder Technol* 44:227, 1985.
9. J Vertommen, A Michoel, P Rombaut, R Kinget. Production of pseudoephedrine HCl pellets in a high shear mixer-granulator. *Eur J Pharm Biopharm* 40:32, 1994.
10. P Holm, O Jungersen, T Schaefer, HG Kristensen. Granulation in high speed mixers. Part 1: Effects of process variables during kneading. *Pharm Ind* 45:806, 1983.
11. HG Kristensen, P Holm, A Jaegerskou, T Schaefer. Granulation in high speed mixers. Part 4: Effect of liquid saturation on the agglomeration. *Pharm Ind* 46:763, 1984.
12. P Holm, O Jungersen, T Schaefer, HG Kristensen. Granulation in high speed mixers. Part 2: Effects of process variables during kneading. *Pharm Ind* 46:97, 1984.
13. A Jaegerskou, P Holm, T Schaefer, HG Kristensen. Granulation in high speed mixers. Part 3: Effects of process variables on the intragranular porosity. *Pharm Ind* 46:310, 1984.
14. A Nagykalldi, L Gyarmati. Untersuchungen zur feuchtgranulation in Diosna-Mischer V25. *Pharm Ind* 42:526, 1980.
15. D Vojnovic, P Selenati, F Rubessa, M Moneghini. Wet granulation in a small scale high shear mixer. *Drug Dev Ind Pharm* 18:961, 1992.
16. N-O Lindberg, C Jönsson, B Holmquist. The granulation of a tablet formulation in a high-speed mixer, Diosna P 25. *Drug Dev Ind Pharm* 11:917, 1985.
17. J Yliruusi, R Tihtonen. High-speed granulation. Part I: Effect of some process parameters of granulation on the properties of unsieved and wet-sieved granules. *Acta Pharm Fen* 98:39, 1989.
18. T Schaefer, P Holm, HG Kristensen. Wet granulation in a laboratory scale high shear mixer. *Pharm Ind* 52:1147, 1990.
19. N-O Lindberg, E Hansson, B Holmquist. The granulation of a tablet formulation in a high-speed mixer, Diosna P25. Influence on intragranular porosity and liquid saturation. *Drug Dev Ind Pharm* 13:1069, 1987.
20. N-O Lindberg, C Jönsson. The granulation of lactose and starch in a recording high-speed mixer, Diosna P 25. *Drug Dev Ind Pharm* 11:387, 1985.

21. T Schaefer, HH Bak, A Jaegerskou, A Kristensen, JR Svensson, P Holm, HG Kristensen. Granulation in different types of high speed mixers. Part 2: Comparison between mixers. *Pharm Ind* 49:297-304, 1987.
22. T Schaefer, HH Bak, A Jaegerskou, A Kristensen, JR Svensson, P Holm, HG Kristensen. Granulation in different types of high speed mixers. Part 1: Effects of process variables and up-scaling. *Pharm Ind* 48:1083, 1986.
23. J Yliruusi, R Tihtonen. High-speed granulation. Part II: Effect of some process parameters on the properties of wet- and dry-sieved granules. *Acta Pharm Fen* 98:53, 1989.
24. HG Kristensen, P Holm, T Schaefer. Mechanical properties of moist agglomerates in relation to granulation mechanisms. Part II. Effects of particles size distribution. *Powder Technol* 44:239, 1985.
25. A Stamm, L Paris. Influence of technological factors on the optimal granulation requirement measured by power consumption. *Drug Dev Ind Pharm* 11:333, 1985.
26. P Holm, T Schaefer, HG Kristensen. Granulation in high-speed mixers. Part VI. Effects of process conditions on power consumption and granule growth. *Powder Technol* 43:225, 1985.
27. P Holm. Granulation in Fielder PMAT 25 VG. PhD dissertation, Royal Danish School of Pharmacy, Copenhagen, 1984.
28. O Wørtz. Production of microgranules for multiparticulate dosage forms. 7th International Conference on Pharmaceutical Technology, Budapest, 9-11 May, 1995, p. 359.
29. P Kleinebudde, L Nymo. Homogeneous pellets of binary mixtures comparison between extruder/spheronizer and high-shear mixer. 7th International Conference on Pharmaceutical Technology, Budapest, 9-11 May, 1995, p. 341.
30. T Schaefer, P Holm, HG Kristensen. Comparison between granule growth in a horizontal and a vertical high speed mixer. I. Granulation of dicalcium phosphate. *Arch Pharm Chem Sci Ed* 14:1, 1986.
31. T Schaefer, P Holm, HG Kristensen. Comparison between granule growth in a horizontal and a vertical high speed mixer. I. Granulation of lactose. *Arch Pharm Chem Sci Ed* 14:17, 1986.
32. LH Christensen, HE Johansen, T Schaefer. Moisture-activated dry granulation in a high shear mixer. *Drug Dev Ind Pharm* 20:2195, 1994.
33. M Ritala, O Jungersen, P Holm, T Schaefer, HG Kristensen. A comparison between binders in the wet phase of granulation in a high shear mixer. *Drug Dev Ind Pharm* 12:1685, 1986.
34. H Rumpf. The strength of granules and agglomerates. In: WA Knepper, ed. *Agglomeration*. New York: Interscience Publishers, 1962, p. 379.
35. GD D'Alonzo, RE O'Connor, JB Schwartz. Effect of binder concentration and method of addition on granule growth in a high intensity mixer. *Drug Dev Ind Pharm* 16:1931, 1990.
36. N Visavrungrroj, JP Remon. Crosslinked starch as binding agent. III. Granulation of an insoluble filler. *Int J Pharm* 69:43, 1991.
37. P Wehrli, P Nobélis, A Cuiné, A Stamm. Response surface methodology: an interesting statistical tool for process optimization and validation: example

- of wet granulation in a high speed mixer. *Pharm Ind* 49:297-304, 1987.
38. D Vojnovic, M Moneghini. Response variables in a granulation process. *Pharm Ind* 49:297-304, 1987.
39. D Vojnovic, M Moneghini. High shear mixer by mixture of wet granulation in a high speed mixer. *Pharm Ind* 49:297-304, 1987.
40. Y Miyamoto, S Ogawa. Evaluation of process variables in a high shear mixer. *Pharm Ind* 49:297-304, 1987.
41. MS Spring. The conductivity of the granulation process. *Drug Dev Ind Pharm* 9:1525, 1992.
42. V Corvari, WC Fry, WL. Shear mixer: evaluation and meter and a strain-gage to Res 9:1525, 1992.
43. J Werani. Production experience. *Drug Dev Ind Pharm* 247, 1988.
44. MJ Cliff. Granulation in granulators: part II. *Pharm Ind* 49:297-304, 1987.
45. MJ Cliff. Granulation in granulators: part I. *Pharm Ind* 49:297-304, 1987.
46. M Kopcha, E Roland, G B. in a high shear mixer/granulation. *Drug Dev Ind Pharm* 247, 1988.
47. DJ Pullen, F Way. Recent 12th Pharm Tech Conf Els.
48. RJ Timko, JL Johnson, G. mixer with a motor slip 1986.
49. J Andersson. N-O Lindberg instruments for measuring *Drug Dev Ind Pharm* 9:14.
50. H Leunberger, B Luy, J S. agglomeration and pelletization. *Drug Dev Ind Pharm* 9:14.
51. H Leunberger. Granulation in a high shear mixer. *Drug Dev Ind Pharm* 9:14.
52. N-O Lindberg, C Jönsson. mixer, Diosna P 25. *Drug Dev Ind Pharm* 9:14.
53. P Holm, T Schaefer, HG V. Power consumption and *Technol* 43:213, 1985.
54. M Ritala, P Holm, T Schaefer. strength on power consumption. *Drug Dev Ind Pharm* 14:1041, 1988.
55. CM Pendharkar, RJ Jhawa. Influence of the specific granulation process using an ins



- Kristensen, JR Svensson, P Holm, HG  
of high speed mixers. Part 2: Com-  
97-304, 1987.
- Kristensen, JR Svensson, P Holm, HG  
of high speed mixers. Part 1: Effects  
Ind 48:1083, 1986.
- ation. Part II: Effect of some process  
dry-sieved granules. Acta Pharm Fen
- mechanical properties of moist agglom-  
ms. Part II. Effects of particles size  
35.
- ical factors on the optimal granulation  
ption. Drug Dev Ind Pharm 11:333,  
granulation in high-speed mixers. Part  
ver consumption and granule growth.  
VG. PhD dissertation, Royal Danish  
or multiparticulate dosage forms. 7th  
cal Technology, Budapest, 9-11 May,  
bellets of binary mixtures comparison  
hear mixer. 7th International Confer-  
apest, 9-11 May, 1995, p. 341.  
comparison between granule growth in  
er. I. Granulation of dicalcium phos-  
986.  
comparison between granule growth in  
ixer. I. Granulation of lactose. Arch  
er. Moisture-activated dry granulation  
rm 20:2195, 1994.  
aefer, HG Kristensen. A comparison  
ulation in a high shear mixer. Drug  
agglomerates. In: WA Knepper, ed.  
Publishers, 1962, p. 379.  
iz. Effect of binder concentration and  
a high intensity mixer. Drug Dev Ind  
starch as binding agent. III. Granu-  
9:43, 1991.  
m. Response surface methodology:  
optimization and validation: example  
of wet granulation in a high-shear mixer. Drug Dev Ind Pharm 19:1637,  
1993.
38. D Vojnovic, M Moneghini, F Rubessa. Simultaneous optimization of several response variables in a granulation process. Drug Dev Ind Pharm 19:1479, 1993.
39. D Vojnovic, M Moneghini, F Rubessa. Drug: Optimization of granulates in a high shear mixer by mixture design. Dev Ind Pharm 20:1035, 1994.
40. Y Miyamoto, S Ogawa, M Miyajima, H Sato, K Takayama, T Nagai. An evaluation of process variables in wet granulation. Drug Dev Ind Pharm 21:2213, 1995.
41. MS Spring. The conductivity of the damp mass during the massing stage of the granulation process. Drug Dev Ind Pharm 9:1507, 1983.
42. V Corvari, WC Fry, WL Seibert, L Augsburg. Instrumentation of a high-shear mixer: evaluation and comparison of a new capacitive sensor, a watt meter and a strain-gage torque sensor for wet granulation monitoring. Pharm Res 9:1525, 1992.
43. J Werani. Production experience with end point control. Acta Pharm Suec 25:247, 1988.
44. MJ Cliff. Granulation end point and automated process control of mixer-granulators: part II. Pharm Technol May:38, 1990.
45. MJ Cliff. Granulation end point and automated process control of mixer-granulators: part I. Pharm. Technol April:112, 1990.
46. M Kopcha, E Roland, G Bubb, WA Vadino. Monitoring the granulation process in a high shear mixer/granulator: an evaluation of three approaches to instrumentation. Drug Dev Ind Pharm 18:1945, 1992.
47. DJ Pullen, F Way. Recent advances in the detection of granulation end-point. 12th Pharm Tech Conf Elsinore, March 30-April 2, 2:182, 1993.
48. RJ Timko, JL Johnson, GW Skinner. Instrumentation of a vertical high shear mixer with a motor slip monitoring device. Drug Dev Ind Pharm 12:1375, 1986.
49. J Andersson. N-O Lindberg. Diosna P 25 high-speed mixer equipped with instruments for measuring the rate of rotation of the main impeller motor shaft. Drug Dev Ind Pharm 9:1495, 1985.
50. H Leunberger, B Luy, J Studer. New development in the control of a moist agglomeration and pelletization process. STP Pharm 6:303, 1990.
51. H Leunberger. Granulation, new technique. Pharm Acta Helv 57:72, 1982.
52. N-O Lindberg, C Jönsson. Granulation of lactose in a recording high-speed mixer, Diosna P 25. Drug Dev Ind Pharm 9:959, 1985.
53. P Holm, T Schaefer, HG Kristensen. Granulation in high-speed mixers, Part V. Power consumption and temperature changes during granulation. Powder Technol 43:213, 1985.
54. M Ritala, P Holm, T Schaefer, HG Kristensen. Influence of liquid bonding strength on power consumption during granulation in a high shear mixer. Drug Dev Ind Pharm 14:1041, 1988.
55. CM Pendharkar, RJ Jhawar, JM Rutledge, W Hause, WM Grim, RJ Harwood. Influence of the specific surface area of selected raw materials on the granulation process using an instrumented mixer. Pharm Technol April:44, 1990.

56. B Richardson. Proceedings of the Interphex Conference 1982, Brighton, United Kingdom.
57. T Schaefer. Equipment for wet granulation. *Acta Pharm Suec* 25:205, 1988.
58. GS Rekhi, R Caricofe, DM Parikh, LL Augsburg. A new approach to scale-up of a high-shear granulation process used in the manufacture of metoprolol tartrate tablet formulations. Pharmaceutical Technology Conference, Oxford, England, March 19th, 1996, vol 2, p. 111.
59. RC Rowe, MD Parker. Mixer torque rheometry—an update, *Pharm Technol Eur* March:27, 1994.
60. GJB Horsthuis, JAH van Laarhoven, RCBM van Rooij, H Vromans. Studies on upscaling parameters of the Gral high shear granulation process. *Int J Pharm* 92:143, 1993.
61. MH Rubinstein. A new granulation method for compressed tablets. *Pharm Pharmacol* 28(suppl):67P, 1976.
62. K Ukita, T Murakami. Preparation of essential oils loaded granule by melt granulation. *Drug Dev Ind Pharm* 20:981, 1994.
63. T Schaefer, P Holm, HG Kristensen. Melt granulation in a laboratory scale high shear mixer. *Drug Dev Ind Pharm* 16:1249, 1990.
64. R Kinget, R Kemel. Preparation and properties of granulates containing solid dispersions. *Acta Pharm Tech* 31:57, 1985.
65. JL Ford, MH Rubinstein. Formulation and aging of tablets prepared from indomethacin-polyethylene glycol 6000 solid dispersion. *Pharm Acta Helv* 55:1, 1980.
66. CM McTaggart, JA Ganley, A Sickmueller, SE Walker. The evaluation of formulation and processing conditions of a melt granulation process. *Int J Pharm* 19:139, 1984.
67. P Flanders, GA Dyer, D Jordan. Drug: The control of drug release form conventional melt granulation matrices. *Dev Ind Pharm* 13:1001, 1987.
68. LJ Thomsen, T Schaefer, JM Sonnergaard, HG Kristensen. Prolonged release matrix pellets prepared by melt pelletization. I. Process variables. *Drug Dev Ind Pharm* 19:1867, 1993.
69. T Schaefer, P Holm, HG Kristensen. Melt pelletization in a high shear mixer. I. Effects of process variables and binder. *Acta Pharm Nord* 4:133, 1992.
70. T Schaefer, P Holm, HG Kristensen. Melt pelletization in a high shear mixer. III. Effects of lactose quality. *Acta Pharm Nord* 4:245, 1992.
71. T Schaefer. Melt pelletization in a high shear mixer. VI. Agglomeration of a cohesive powder. *Int J Pharm* 132:221, 1996.
72. T Schaefer, C Mathiesen. Melt pelletization in a high shear mixer. VII. Effects of product temperature. *Int J Pharm* 134:105, 1996.
73. J Lüdemann. Smeltzgranulierung-eine lösemittelfreie Alternative, APV-Seminar: Granulierung-Eintopfverfahren und andere aktuelle Trends, Darmstadt 17-18 June, 1996, p. 1.

## 8

### Low Shear Granulation

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#### I. INTRODUCTION

- A. Comparison of Granulation Processes
- B. Binder Issues

#### II. MECHANICAL AGITATION

- A. Ribbon or Paddle Mixers
- B. Planetary Mixer
- C. Orbiting Screw Mixers
- D. Sigma Blade Mixers

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- A. Bar Speed and End Point
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#### IV. SCALE-UP

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#### REFERENCES

\*Current affiliation: Fleming Inc.,

Conference 1982, Brighton, United

Acta Pharm Suec 25:205, 1988.

gsburger. A new approach to scale-  
d in the manufacture of metoprolol  
al Technology Conference, Oxford,

ometry—an update, Pharm Technol

BM van Rooij, H Vromans. Studies  
near granulation process. Int J Pharm

hod for compressed tablets. Pharm

essential oils loaded granule by melt  
1994.

lt granulation in a laboratory scale  
5:1249, 1990.

erties of granulates containing solid  
.

nd aging of tablets prepared from  
olid dispersion. Pharm Acta Helv 55:

r, SE Walker. The evaluation of for-  
melt granulation process. Int J Pharm

he control of drug release form con-  
nd Pharm 13:1001, 1987.

, HG Kristensen. Prolonged release  
ion. I. Process variables. Drug Dev

pelletization in a high shear mixer.  
Acta Pharm Nord 4:133, 1992.

pelletization in a high shear mixer.  
Nord 4:245, 1992.

hear mixer. VI. Agglomeration of a  
996.

n in a high shear mixer. VII. Effects  
05, 1996.

nittelfreie Alternative, APV-Seminar:  
e aktuelle Trends, Darmstadt 17–18

## 8

# Low Shear Granulators

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## I. INTRODUCTION

Shearing of the powder bed occurs in all granulators. The low shear granulators included in this chapter are granulators that for reasons of agitator speed, sweep volume, or bed pressures generate less shear than granulators discussed in other chapters, such as extruders or the high shear mechanical granulators. Also considered to be low shear, but covered in other chapters, are the fluid bed granulators.

### A. Comparison of Granulators

Comparing final granule characteristics in fluid bed, low shear, and high shear applications is problematic because it is often difficult for the same formulation to be successfully processed in each piece of equipment. However, some broad conclusions may be drawn. Two of the characteristics most frequently reported are bulk density and particle size; therefore, a comparison will be shown for these characteristics. These granulators may have the same operation, but the final product produced may be very different. The differences are seen in the length of time required to accomplish the wet granulation operation. The process of wet granulation involves three steps; blending, liquid binder addition, and wet massing or distribution of the liquid. After charging the powder to the mixer, a blending step is required to achieve a homogeneous blend. The time required to achieve the blend depends on the amount of movement achieved in the unit and the size of the unit. Also, the degree of homogeneity differs from one type of mixer class to the next. In some classes of blenders, the one can easily overblend and segregate different components of the mix.

The binder solution addition step follows the blending step. The selection of the type of binder and quantity depends on the type of mixer selected for the wet granulation. Nouh [1] studied a sulfadiazine formulation using several different binders. He worked in both a fluid bed unit and a conventional wet massing–screening method. When using 5% gelatin as a binder, he noted a 0.968-mm–average granule size in wet massing and 0.574 mm in the fluid bed. The wet-massed product is larger. For acacia as binder at the 5% level, the values were 0.901 mm for wet massing and 0.605 for the fluid bed. For a polyvinyl pyrrolidone (PVP) binder at the 5% level, the wet massing produced 0.962-mm–average granule size versus 0.247 mm for the fluid bed. Surprisingly, the difference between the methods did not transfer to the bulk density results. Both the acacia and PVP formulations had similar bulk densities in both methods. The gelatin did show a difference, yielding 0.476 g/mL for the wet massing and 0.294 g/mL for the

fluid bed. Gore et al. [2] made a comparison of a planetary mixer, and a high shear granulator. The yield—reduced large and small granules—was 97.7% in the fluid bed, 53% in the high shear granulator. The bulk density was 0.71 g/mL, respectively. For a 100-L (27-gal) vessel, Scarpone et al. [19] found 80% granulation in a 2-m<sup>3</sup> (2-ft<sup>3</sup>) vessel and 50.7% granulation in a 1-m<sup>3</sup> (27-gal) vessel. The measurements averaged 0.4 g/mL for the fluid bed drug formulation in the small vessel. The work that the bulk density of the granulator is intermediate in value between the fluid bed and high shear granulator.

Similar conclusions may be drawn from the high shear granulators produce fluid bed granulators. A final note regarding the tumbling granulator has a rotation speed expected as the material flows

### B. Binder Issues

Because of improved liquid distribution in high shear granulators require less liquid mixer. Liquid requirement for a horizontal mixer, was 4.5% of the granule weight required for a lower shear planetary mixer. This also densify granules, such as the sigma mixer is slightly reduced. This indicates that dissolving a solid binder in the liquid adding the solid binder to the liquid dried granule hardness [3].

The final stage of wet granulation is wet massing. This step can be used to fill the voids between granules and densify the granules. The final density of the granules is a function of the amount of shearing available during the mixing process by mechanical means. These low shear mixers cannot provide the sole by mechanical means of granules of some integrity.

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shows the blending step. The sequence depends on the type of mixer studied a sulfadiazine formulation in both a fluid bed unit and a fluid bed. When using 5% gelatin as a binder the particle size in wet massing and 0.574 mm for acacia as binder for wet massing and 0.605 for PVP) binder at the 5% level, the granule size versus 0.247 mm difference between the methods did not exist for the acacia and PVP formulations. The gelatin did show a difference in wet massing and 0.294 g/mL for the

fluid bed. Gore et al. [2] made a comparison among a fluid bed granulator, a planetary mixer, and a high shear granulator. They found that the granule yield—reduced large and small fractions—between 20 and 100 mesh was 97.7% in the fluid bed, 53.3% in the planetary mixer, and 71.8% in the high shear granulator. The respective bulk densities were 0.39, 0.66, and 0.71 g/mL, respectively. For comparison, in low shear tumble granulator, Scarpone et al. [19] found 84% yield between 20 and 100 mesh in a 0.05-m<sup>3</sup> (2-ft<sup>3</sup>) vessel and 50.7% yield in a 2.83-m<sup>3</sup> (100-ft<sup>3</sup>) vessel. Density measurements averaged 0.486 g/mL for the two trials of a cardiovascular drug formulation in the smaller vessel. It is apparent from the foregoing work that the bulk density values produced in a low shear, tumbling granulator is intermediate in value between those of a fluid bed and a high shear granulator.

Similar conclusions may be drawn about granule morphology as lower shear granulators produce fluffier, more porous granules than do high shear granulators. A final note related to morphology is that if the low shear, tumbling granulator has a rotating shell, some rounding of granules may be expected as the material flows through the angle of repose.

## B. Binder Issues

Because of improved liquid distribution early in the granulation process, high shear granulators require 60–80% of the liquid needed in a low shear mixer. Liquid requirement for an antacid granulation made in a high shear horizontal mixer, was 4.5% of the total batch, whereas 7% liquid was required for a lower shear planetary mixer. Some of the low shear granulators also densify granules, such as the sigma mixer. The liquid requirement for the sigma mixer is slightly reduced at 6% for the same antacid. Some studies indicate that dissolving a solid binder and adding it to the dry mix versus adding the solid binder to the dry mix and then wetting the mix increases dried granule hardness [3].

The final stage of wet granulation process is the liquid distribution or wet massing. This step can be compared with a kneading step during which the voids between granules are compressed and thereby, the granules are densified. The final density of the granules, therefore, is dependent on the amount of shearing available in the unit. Because the shear is introduced in the mixing process by mechanical means by moving impeller or blades, these low shear mixers cannot compress the voids between the wet granules solely by mechanical means and thus require more binder solution to form granules of some integrity.

## II. MECHANICAL AGITATOR GRANULATORS

The machine classes to be considered under mechanical are

1. Ribbon or paddle blender-granulators
2. Planetary mixer
3. Orbiting screw mixer
4. Sigma blade mixer

### A. Ribbon or Paddle Blenders

The ribbon blender type mixer (Fig. 1) is very popular as a dry mixer. However, if small amounts of liquids are added or if a dry paste is formulated for the machine, the ribbon blender can serve as a very reliable granulator [3]. Most ribbon blenders are not made to withstand the shaft torque required for manufacturing granules. One should assure that the granulator shaft is strong enough before granulating in a ribbon blender designed to dry mix.

Zoglio et al. [3] studied several kneading times in a chopper ribbon blender and discovered an optimum range of kneading times for providing the best granule mechanical properties. A kneading time that is too long densifies the granules. This increases moisture exposure, particle size, wet paste appearance, and reduces porosity. The tendency of the material to stick to the side wall is pronounced in the ribbon blender.

Paddles instead of ribbons decrease sticking problems and the torque required. Paddle blenders as batch granulators can handle wetter paste. These

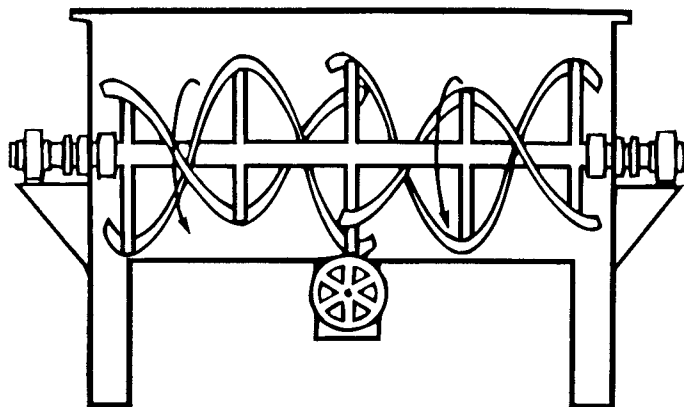


Fig. 1 Ribbon blender.

## Low Shear Granulators

paddle blenders are occasionally used for granulation, both lower torque and more gentle mixing. The movement of the paste is gentle, and the formulation of a nontacky paste is possible. Crystalline cellulose, that helps in granulation, is plastic and nonsticky.

Two very popular ribbon blenders are the topogranulator and the topomixer.

The topogranulator (Fig. 2) is a batch granulator with the ability to either compress or knead the material. Compression while slightly reducing the particle size of the granules, but it does not reduce density if used during the drying process. The topogranulator is also a batch granulator.

The topogranulator is used for granulating by liquid addition under vacuum. The topogranulator method uses liberated moisture (from the reaction of acid) to start the acid-base reaction. The granulating of the sodium bicarbonate is completed. The water produced is removed from the reaction. The topogranulator granulates the particles into the binding moisture. The granules with a lower moisture content are dried. The drying removes the water from the granules, making the process more reproducible.

Granulating in vacuum is a batch process. Liquid addition into the vacuum chamber is done during the drying process. This granulator is used for granulating a calcium carbonate-based material.

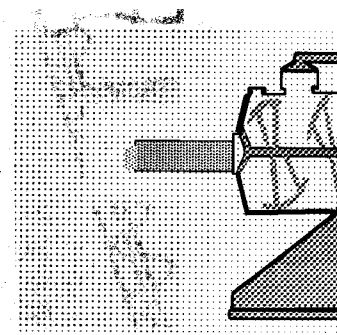


Fig. 2 Topogranulator.

## GRANULATORS

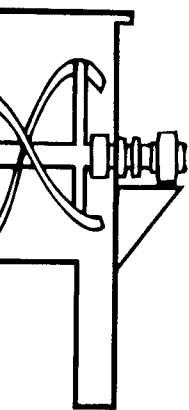
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granulators

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loading times in a chopper ribbon e of kneading times for providing A kneading time that is too long isture exposure, particle size, wet e tendency of the material to stick n blender.

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paddle blenders are occasionally used as continuous granulators and have both lower torque and more applications than a continuous ribbon blender. The movement of the paste helps remove material from the paddles. Formulation of a nontacky paste is aided by using a substance, such as microcrystalline cellulose, that helps absorb the excess moisture from the mix, yet is plastic and nonsticky.

Two very popular ribbon or paddle blenders used as granulators are the topogranulator and the turbulizer.

The topogranulator (Fig. 2) is a batch-style ribbon blender granulator with the ability to either compress or mechanically fluidize the granulation. Compression while slightly wet increases the overall influence in the liquid on the particle size of the granulation. At the other extreme, fluidization reduces density if used during the granule growth phase or speeds drying. The topogranulator is also a vacuum dryer.

The topogranulator is used extensively to make effervescent products by liquid addition under vacuum or by the Murry fusion method [4]. Murry's method uses liberated moisture from the acid in the mix (i.e., hydrous citric acid) to start the acid-base reaction, which generates more water. Thus, granulating of the sodium bicarbonate-citric acid mixture can be accomplished. The water produced must be removed quickly to reproducibly stop the reaction. The topogranulator, because of its ability to compress the particles into the binding moisture, makes a larger, more dense granulation, with a lower moisture content. Also, mechanical fluidization and vacuum drying removes the water from the reaction more quickly, making the process more reproducible.

Granulating in vacuum removes entrapped air from the particle surface. Liquid addition into the vacuum provides immediate wetting and also begins the drying process. This granulation in vacuum allows the manufacturing of a calcium carbonate-based effervescence with rapid reactivity.

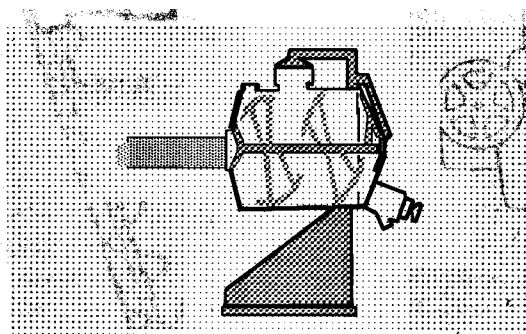


Fig. 2 Topogranulator.

The turbulizer is a continuous paddle granulator. By using continuous powder feeders and liquid-metering pumps, the unit produces large quantities of product per hour in a very small space. The unit provides adjustable mixing, shear, and impact action based on the revolutions per minute (rpm) of the shaft and angle of the impact blade. The paddle adjustments also vary the retention time. The machine has a very low silhouette. Paddles are easily accessible for cleaning and inspection either through a clam shell- or drop door shell-opening side wall. The unit is jacketed for material temperature control.

Another continuous paddle granulator, made by Teledyne Readco, has been studied by Ghali et al. [5]. The unit is adjustable to produce either low- or high-shearing action. The amount of energy induced by the rotating shaft can be selected by using various types of pins. A rounded granule results from the action of the pin tip speed and some rolling of the granulation against the fixed vessel wall.

### B. Planetary Mixer

The planetary motion of these granulators is created by rotating the agitator off an assembly in a direction opposite that of the rotation of the agitator assembly as it moves around the bowl. The planetary mixers (Fig. 3) are represented by many commercial names, Hobart, Kitchen Aide, Pony, and AMF Glen granulators. All of these mixers have the same basic makeup

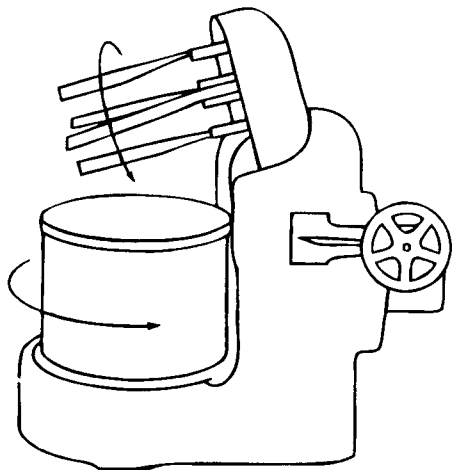


Fig. 3 Pony mixer.

### Low Shear Granulators

which includes (a) planetary agitators.

These mixers tend to be more effective in the horizontal plane than in the vertical. Large quantities of material tend to be dumped and readded. Reduced vertical mixing is necessary to prevent the materials from causing the materials to adhere to the walls, which leads to vertical stratification.

Remon and Schwartz, [6] studied the granulation of moist mixtures in a planetary mixer. They found that with increasing massing time, the binder distribution and mechanical properties of granule growth in

### C. Orbiting Screw Granulator

The orbiting screw granulator is a continuous granulator. However, the unit has been used for drying and cooling to add liquids to dry powders or cooling. A sintered metal coating is applied to the skin of the mixer or extruder. The unit has added features, along with a heating jacket, which make it an effective granulator for granulating. The unit is a very gentle granulator.

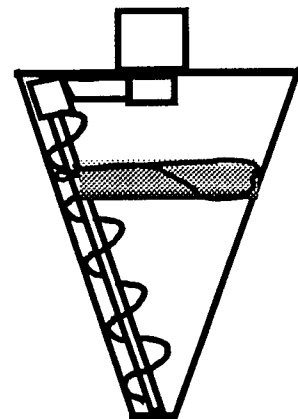


Fig. 4 Orbiting screw mixer.



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s, the unit produces large quanti-  
pace. The unit provides adjustable  
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The paddle adjustments also vary  
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of energy induced by the rotating  
types of pins. A rounded granule  
ed and some rolling of the granu-

is created by rotating the agitator  
hat of the rotation of the agitator  
The planetary mixers (Fig. 3) are  
Hobart, Kitchen Aide, Pony, and  
ers have the same basic makeup

which includes (a) planetary motion, (b) removable bowl, and (c) top-drive agitators.

These mixers tend to be better at mixing dry powders in the horizontal plane than in the vertical. Lack of vertical mixing may require the materials to be dumped and readded to the bowl to obtain an acceptable dry mix. Reduced vertical mixing is much less a problem in the wet-mix phase, because the materials adhere to the agitator and move in groups without vertical stratification.

Remon and Schwartz, working with microcrystalline cellulose and lactose mixtures in a planetary mixer, saw decreased friability of the granule with increasing massing time [6]. This increased massing time increases binder distribution and mechanical strength. Ghanta demonstrated the mechanism of granule growth in a Hobart mixer [7].

### C. Orbiting Screw Granulator

The orbiting screw granulator (Fig. 4) is also used mainly for dry mixing. However, the unit has been fitted with a nozzle through the center agitator to add liquids to dry powders [8]. Also, a jacket can provide both heating or cooling. A sintered metal plate can allow entry of compressed air through the skin of the mixer or exhaust moisture to obtain drying. All of these added features, along with a chopper in the side wall, allow this blender to be an effective granulator for powders, slurries, suspensions, and paste. The unit is a very gentle granulator mixer.

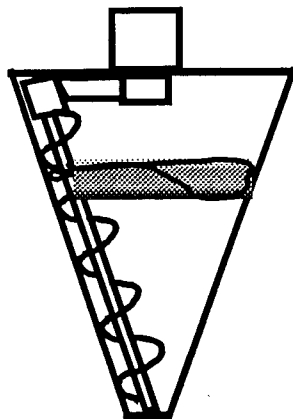


Fig. 4 Orbiting screw mixer.

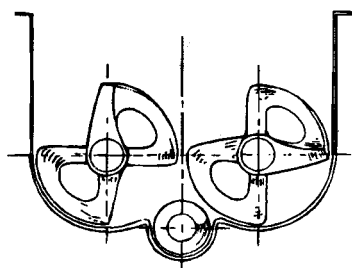
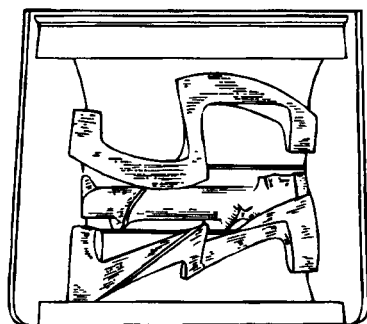


Fig. 5 Sigma blade mixer.

#### D. Sigma Blade Mixer

The sigma blade mixer (Fig. 5) is a compressive granulator. Generally, it develops materials into a paste- or dough-type consistency. Often the sigma blade mixer is preceded by a dry mixer. The unit generates liquid distribution with pressure during granulating. This creates a uniform granulation with binder matrix and good binder distribution.

### III. ROTATING SHAPE GRANULATORS

The vessel shapes are usually some derivation of a cylinder, with a double cone and V-shape (Fig. 6) being the most common examples. Unlike their fluid bed and high shear counterparts, the machine shells rotate about an axis parallel to the ground. The rotation speed is more moderate, and generally falls into a range of 72.2–106.7-m (250–350 ft)/min (mpm; fpm) peripheral speed. The revolutions per minute (rpm) change as vessel size grows. A laboratory model may rotate at 25–30 rpm, whereas a larger pro-

#### Low Shear Granulators

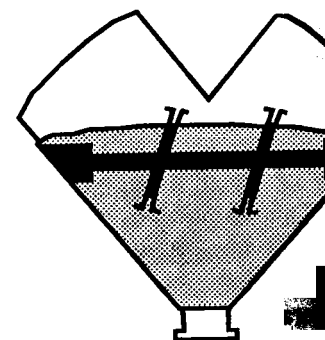
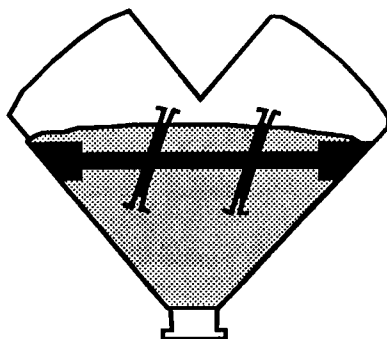


Fig. 6 Schematic of the twin shell granulator. (Courtesy of 1 Stroudsburg PA.)

duction model may rotate at 25–30 rpm and is often a factor in scale-up.

A second rotating device is often used in the shell. This bar or arm may be driven with support only on a single point, adding more energy into the system. The second bar is driven by an additional motor. The manufacturer's agitator or intensifier bars, which are induced by the shell mover, provide additional mixing. This should not be confused with the shell mixer. This produces mainly a convective mixing. The machines were originally designed for convective mixing. Only a few are granulator-dryers.

The increased peripheral speed with the vessel's peripheral speed is often a factor in scale-up. The shell also serves as liquid addition and cooling if there is a need. The machines are vacuum capable, which makes them a single-pot processor for many applications. The higher size constraints make them have many parts and must become increasingly unwieldy.



**Fig. 6** Schematic of the twin-shell blender that allows blending and granulating in a single vessel. (Courtesy of Patterson-Kelley Co., Division of Harsco Corp., East Stroudsburg PA.)

duction model may rotate at 4–8 rpm. The peripheral speed remains constant and is often a factor in scale-up.

A second rotating device is located on the same axis of rotation as the shell. This bar or arm may be supported at both ends or may be cantilevered, with support only on a single end. The bar is used to impart substantially more energy into the system than that delivered by the rotating shell. The bar is driven by an additional, larger motor that runs independently of the shell motor. The manufacturers descriptive names for these bars, such as agitator or intensifier bars, confirm their use. Unlike the gentle rolling action induced by the shell movement, the bar movement has a high-speed nature. This should not be confused with high shear, because the bar movement produces mainly a convective motion within the material. Indeed, these machines were originally designed as mixers, with elements of diffusive and convective mixing. Only later in their evolution did they become granulator-dryers.

The increased peripheral speed of the bar is substantial when compared with the vessel's peripheral speed. As a general rule, they operate at ten times the speed of the shell or about 914.4 mpm (3000 fpm). The bars may also serve as liquid addition devices. The vessels may be jacketed for heating and cooling if there is a necessity for these options during granulation. They are vacuum capable, which makes them candidates for increasingly popular single-pot processor for mixing, granulating, and drying in the single vessel. The higher size constraint is usually due to the weight of the bar. The bars have many parts and must be disassembled often for cleaning. Larger bars become increasingly unwieldy and difficult to remove from the interior of

the vessel. Some manufacturers offer clean-in-place systems that at least provide the potential to automate the cleaning process.

Ample opportunity exists for fine-tuning a granulation process in these machines. Apparatus variables that can be adjusted are shell speed, bar speed, bar size, and bar design. Process changes can be made in mix time, liquid addition time, bed temperature, internal vessel pressure, and droplet size.

Overwhelmingly, these granulator types are used in batch granulators. However, a few manufacturers offer continuous-granulating systems that emulate the combination of forced and rolling agglomeration found in the batch machines. Beside the obvious problems of validating a continuous process, throughput requirement is usually the influencing criterion when considering a change from batch to continuous operation.

Much of the granulation done in the pharmaceutical industry is by wet massing and, more recently, by fluidized bed [9]. Consequently, the literature is rich with articles describing the many permutations studied in these machines. On the other hand, the rotating shape granulators originated as mixing devices and a paucity of basic research articles exist on their usage as granulators. This certainly makes them a fruitful area for future research.

### A. Bar Speed and Energy Input

The influence of agitator bar speed and its accompanying energy input yields a wide influence on the physical properties of the granulated material. Watano et al. [10], using a fluidized bed granulator with an agitator blade, varied the rotation speed of the agitator and observed the effect it had on product density. They were able to derive a predictive equation that yielded the density value when the agitator speed was known. The same group measured *shape index*—the mean ratio of the short/long diameters—and concluded that as granulation time increased, the shape tended more toward sphericity. The rotating shape granulators vary energy input to the powder bed by changing the agitator speed or extending the running time of the bar after liquid addition has stopped. A common term for the extended bar period is postmix time.

Postmix times from 1 to 8 min were studied in an experiment that used a corn syrup binder to agglomerate a powder component [11]. The vessel was an 7.6-L (8-qt) agglomerator with a V-shaped design. A typical postmix time in this vessel size is 2–3 min. The experimental results showed a moderate increase in yield from 1 min through 3 min. Beyond 3 min, the yield remained relatively constant through 8 min. The oversized fraction peaked at 1 min and declined with each successive minute. Concomitantly, the undersized fraction was smallest at 1 min and increased gradually

## Low Shear Granulators

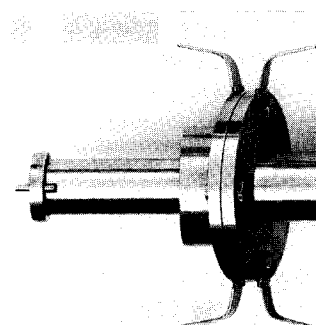
through 8 min. Density showed indication of the amount of temperature accrued from 1 min.

The results are readily interpreted. The oversized (probably oversized) distribution by the bar action. Larger granules were subjected to more erosion after liquid addition. Eroded particles were minimized. Known volume.

Further studies considered peripheral speeds of 971 m/s. This value. Similar particle size distribution, but the 50% speed yielded smaller granules. Obviously, to adequately distribute the 100 and 75% speeds indicated. Investment in the pilot plant process at a minimum.

### B. Disk Size and Bar Design

Addition of binder liquid via granulators. The double-coat and spray head combination designs exist for the more



**Fig. 7** Intensifier bar for the Kelley Co., Division of Harsco

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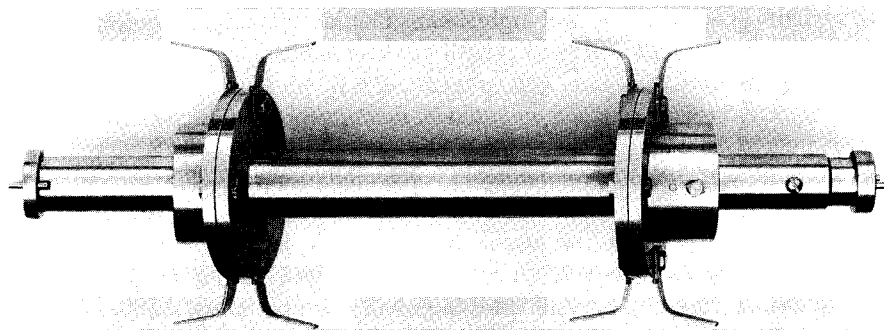
through 8 min. Density showed a rise as postmix time increased and, as an indication of the amount of energy imparted, a 5.6°C (10°F) rise in bed temperature accrued from 1 to 8 min postmix time.

The results are readily explainable. As postmix time increases, any oversized (probably overwet) granules were subject to breakdown and redistribution by the bar action. The undersized fraction increased because larger granules were subject to attrition and had a difficult time reagglomerating after liquid addition had ceased. Density rises because larger, more dense, particles were minimized, allowing more material to pack into a known volume.

Further studies considered bar speed. Experiments were conducted at peripheral speeds of 971 mpm (3186 fpm) and at values of 75 and 50% of this value. Similar particle size profiles were noted for the 100 and 75% speed, but the 50% speed showed a large increase in oversized and undersized granules. Obviously, the lowest bar speed was not energetic enough to adequately distribute the binder solution. The commonality of results at 100 and 75% speeds indicates that variable-speed drive studies may be a wise investment in the pilot laboratory, allowing one to fine-tune a granulation process at a minimum level of energy expenditure.

## B. Disk Size and Bar Design

Addition of binder liquid with spray heads is available with rotating shape granulators. The double-cone shape is often used with a dry intensifier bar and spray head combination for granulating (Fig. 7). A wide range of bar designs exist for the more typical situation of adding liquid through the bar;



**Fig. 7** Intensifier bar for the twin-shell blender/granulator. (Courtesy of Patterson-Kelley Co., Division of Harsco Corp., East Stroudsburg PA.)

blade or knife design is one variable to consider. The blades extend perpendicularly from the disk circumference and then bend 90° in a shape often called a "dog-eared" design.

The blade shape is critical for the liquid addition method. As the blades rotate, they carve out a toroidal void volume in the flowing powder bed. The liquid exiting the disk coats the interior of the torus. Proper vessel loading ensures that the liquid does not reach the vessel walls.

The action of the blades is quite vigorous and may cause a problem with very friable raw materials. A modification to the bar that removes the blades and recesses all nuts and bolts can be used to granulate these fragile materials. Further fine-tuning of the spray pattern can be accomplished with changes in the positioning of liquid evacuation spacing on the disk circumference. A straight pattern creates droplet flow orthogonal to the axis of rotation, yielding only a small area of the interior torus being coated. An angled pattern creates a substantially wider spray effect, with more efficient droplet distribution.

Disk diameter is critical: a large diameter disk imparts more energy as torque is a function of diameter. The larger diameter offers more circumference for liquid to be evacuated and carves out additional void volume in the material. The sweep volume of the disks is considered a major factor in properly scaling-up a granulator.

### C. Liquid Addition Rate

Particle motion is so complex when granulating that it becomes difficult to determine the optimum rate of liquid addition. Paris and Stamm [12] studied rates of 5, 10, and 20 mL/min in a fixed shell, helicoidal mixer with vertical bar, and determined that the best results occurred at the slowest rate.

Cliff [13], working in a high shear granulator, found that a long binder addition time was needed to prevent overdensification. Lipps and Sakr [14], using a top-spray, fluidized bed granulator, related geometric mean granule size, specific surface area, and granule flow properties, to the binder flow rate. In high shear granulators, lowered granule porosity is a function of binder addition time. The rotating shape granulators coat the interior of the bar-induced torus. Liquid is literally ripped into droplets by the peripheral speed of the bar. Tumbling action ensures fresh material replaces the wet material during each shell revolution [15]. In a study using a rotating shape granulator, corn syrup was added to a powder component at 1300, 610, and 248 g/min. The highest rate was self-regulating, in that the liquid was placed in a funnel and allowed to flow by gravity into the bar. The 610-g/min rate was used as a typical rate, and the slowest rate was substantially lower than typical. As expected, the product yield and reduced oversized and undersized

fractions improved as the liquid addition rate increased. At a typical rate. A small increase in the slowest rate. An extremely slow liquid addition rate.

Apparently, when one continues to abrade the granules, the granules can be rewetted and the particle. This mechanism tends to offset the expected increase in the

Extremely rapid liquid addition to the system. Many particles are associated with the droplets. A concentrated onrush of liquid. The addition rate is that liquid may create a backpressure situation develop and ultimately cause it to move to the interior of the machine. Because the machine is jacketed, the potential exists for a hard granule.

Use of the dissolved binder could be detrimental. Any variation in spacings on the disk. Also, 40–50 cp may not atomize.

### D. Droplet Size

Droplet size is a very important factor. Droplet size is unimportant in high shear granulators. The distribution of droplet size readily distribute and redispersible. The design of rotating shape granulators is unique. The design of the device or agitator bar. Any change in the design would mean that liquid would

The liquid in a rotating granulator exits in the interior of the torus. The device used for metering the flow, the speed of rotation of the bar, the placement of the bar to draw in the liquid, the placement of spacers that would exceed this thickness value, and the spacer openings are 0.025 in.

consider. The blades extend perpendicular then bend 90° in a shape often

liquid addition method. As the blades rotate in the flowing powder bed, the interior of the torus. Proper vessel design touches the vessel walls.

agorous and may cause a problem with rotation to the bar that removes the binder. It can be used to granulate these fragile particles. A pattern can be accomplished with varying spacing on the disk circumference. The flow is orthogonal to the axis of rotation, the interior torus being coated. An atomization spray effect, with more efficient

the larger disk imparts more energy as the diameter offers more circumference. It evacuates out additional void volume in the granules. This is considered a major factor in

rotating that it becomes difficult to control. Paris and Stamm [12] studied a helical, helicoidal mixer with vertical rotation. It occurred at the slowest rate.

granulator, found that a long binder residence time was necessary for granule densification. Lipps and Sakr [14], related geometric mean granule size properties, to the binder flow rate. Granule porosity is a function of granulator design. Granulators coat the interior of the disk into droplets by the peripheral spray. Fresh material replaces the wet granules. In a study using a rotating shape granulator component at 1300, 610, and 300 rpm, in that the liquid was placed into the bar. The 610-g/min rate granule rate was substantially lower than the reduced oversized and undersized

fractions improved as the liquid rate moved from the rapid addition to the typical rate. A small increase in yield can be noted from the typical rate to the slowest rate. An extremely small oversized fraction may be noted with the slow liquid addition rate.

Apparently, when one extends the liquid addition period, the bar continues to abrade the granules. Favorably, any particles that have been fractured can be rewetted and the fracture surface can easily bind to another particle. This mechanism tends to hold down the oversized fraction, without the expected increase in the undersized fraction.

Extremely rapid liquid addition overwhelms the blending capability of the system. Many particles simply do not have enough time to become associated with the droplets, whereas others become overwet with the concentrated onrush of liquid. An additional consequence of a high liquid addition rate is that liquid may have difficulty in releasing from the bar. A backpressure situation develops that may impede liquid flow in the feed tube and ultimately cause it to reverse its flow. High enough backpressure can induce a spring-loaded bar to jump from its moorings and damage the interior of the machine. Because the rotating shape generators are often heat-jacketed, the potential exists for them to provide a partially or fully coated, hard granule.

Use of the dissolved binder addition method through an agitator bar could be detrimental. Any undissolved solids may clog the liquid evacuation spacings on the disk. Also, binder solutions with a viscosity much beyond 40–50 cp may not atomize readily when released from the disk.

#### D. Droplet Size

Droplet size is a very important variable in fluidized bed granulation. Droplet size is unimportant in high shear granulators because the energy exists to readily distribute and redistribute the liquid. Liquid addition in the rotating shape granulators is unique, for the droplets are released from the fluidizing device or agitator bar. An analogous situation in a high shear application would mean that liquid was being added through the impeller or chopper.

The liquid in a rotating shape granulator is fed through a tube and exits in the interior of the bar through a distribution slot. A pump can be used for metering the flow, or gravity flow may be sufficient, if desired. The speed of rotation of the bar actually induces an area of lower pressure within the bar to draw in the liquid. The liquid exits the agitator bar through openings on the circumference of the rotating disk. Openings can be adjusted by placement of spacers that vary in thickness. A droplet diameter cannot exceed this thickness value, although smaller droplets may be present. Typical spacer openings are 0.025 cm (0.010 in.) with common adjustment to 0.0127

(0.005) and 0.05 cm (0.020 in.), depending on the viscosity of the liquid. Returning to the previous corn syrup study, it was noted that little difference was seen in yield, or in oversized and undersized fractions, when the spacing of 0.0127 (0.005) and 0.025 cm (0.010 in.) were compared. The 0.05 cm (0.020 in.) spacing showed considerable deterioration in yield and a large oversized fraction, probably caused local overwetting.

Many granulation methods deliver the liquid at some pressure through a spray head. With liquid addition through the bar, only enough pressure is needed to overcome line loss. Undue pressure is actually counterproductive. The atomization is affected, and the liquid exiting the disks tends to be sheet-like rather than the easier distributed droplets.

Droplet size in a fluid bed has been measured by capturing droplets on a slide covered with viscous oil. The size has been determined to be in the 20- to 100- $\mu\text{m}$  range, depending on the rate of fluid addition [16]. Less delicate techniques in the rotating shape granulator have shown droplet sizes of about 250  $\mu\text{m}$ .

### E. Vessel Loading

A negative factor for rotating tumble agglomerators with high-speed internal bars is the tight constraint for fill level. This level is often 50–60% of the total volume, and the powder level must have some contact with the bar. Overloading the vessel impedes the mixing action.

Underloading causes the material to flow beneath the bar during vessel rotation, resulting in liquid spraying on the shell wall. This can be a factor in material sticking during the drying phase.

Even careful loading of the machine with the dry powder may not be sufficient to preclude spraying through to the walls. If substantial densification occurs during early liquid addition, the load may drop enough during the final stages of liquid addition for liquid to find its way to the shell wall.

### F. Low Shear Single-Pot Processing

The rotating shape granulators offer fine potential for single-pot processing (Fig. 8). Their original design as mixers ensures even minor ingredients are well distributed in the dry mix phase before granulation. After granulation, the heated shell and vacuum capability are used for gentle tumble drying and collection of the condensed vapors. The bar can then be used to provide a measure of dry sizing, followed by lubricant addition and tumble blending.



g on the viscosity of the liquid. It was noted that little difference in droplet sizes, when the spacing (0.05 cm) were compared. The 0.05 cm spacing showed no deterioration in yield and a large improvement in wetting.

liquid at some pressure through the bar, only enough pressure is applied so that the liquid is actually counterproductive. Increasing the disks tends to be sheet-like.

measured by capturing droplets. The droplet size has been determined to be in the range of 100-200 microns at a rate of fluid addition [16]. Less granulation have shown droplet sizes

granulators with high-speed internal mixing. The mixing level is often 50-60% of the total volume. They have some contact with the bar. The mixing action.

flow beneath the bar during vessel operation. This can be a factor in the design.

with the dry powder may not be sufficient to fill the walls. If substantial densification is required, the load may drop enough during operation to find its way to the shell wall.

potential for single-pot processing. The process requires even minor ingredients are added during granulation. After granulation, the granules are used for gentle tumble drying. The granules can then be used to provide a controlled addition and tumble blending.

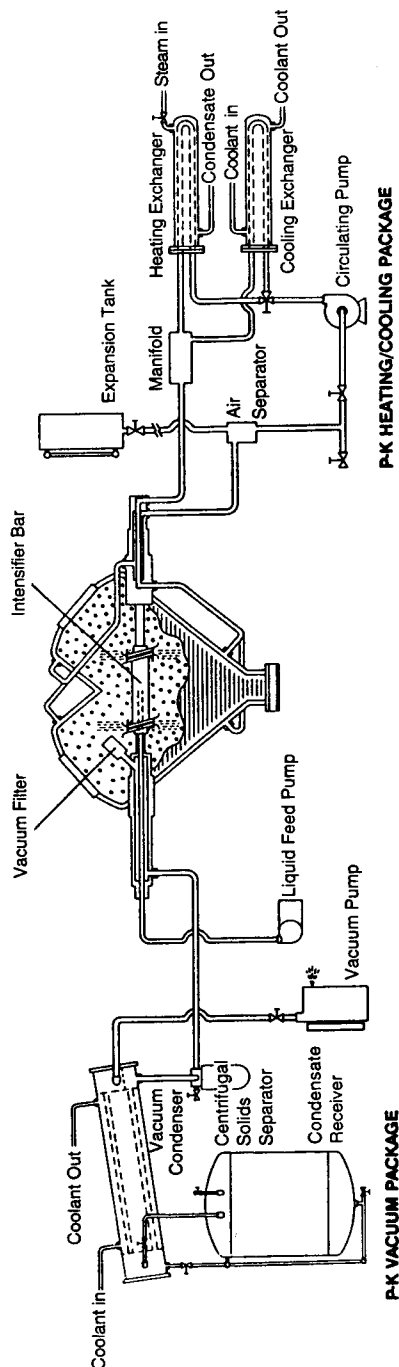


Fig. 8 Schematic diagrams of Patterson-Kelley Solids Processor. (Courtesy of Patterson-Kelley Co., Division of Harsco Corp., East Stroudsburg PA.)

### G. Continuous Granulation

Although batch granulation is commonly used, there are some examples of low shear continuous granulation. A true adaptation of the batch, rotating shape granulators is the Patterson Kelley Zig-Zag mixer (Figs. 9 and 10). This vessel consists of a high-speed-mixing chamber connected to a series of three V-shaped tumble blenders. The principles of fluid addition and disk speeds covered earlier are equally applicable to the Zig-Zag. The typical hold-up volume is half of the total volume of the vessel.

The hold-up volume can be adjusted somewhat by raising or lowering the discharge end a few degrees from the horizontal. Residence times are in the 3- to 5-min range for granulation applications. Two types of granulation mechanisms occur in this machine. When material is in the high-speed-mixing chamber, the liquid droplets contact the powder in a manner similar to that of the batch units. As the wetted material travels into the tumbling section, rolling agglomeration occurs. The tumbling section splits its load in half on each revolution, allowing half the material to proceed forward while the other half recycles to the rear. This action tends to smooth out any feeding inconsistencies.

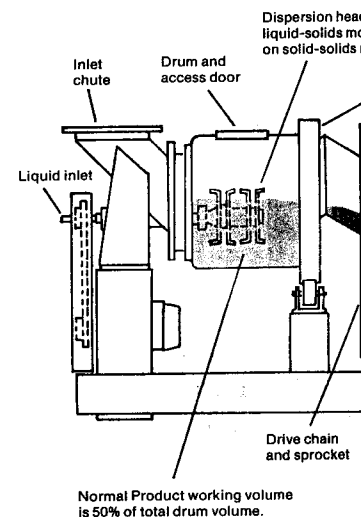
Scale-up to larger Zig-Zag units is based on constant residence times. Therefore, even in the very largest models, a residence time of 3–5 min can be expected. The largest models are capable of producing 30,000 kg/h.

## IV. SCALE-UP

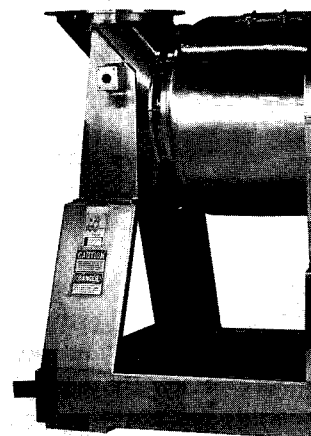
Arguably, the most difficult part of implementing a granulation process is the scale-up step. The many variables involved and the poorly understood relations among the variables often places scale-up in the realm of trial and error. Hancock et al. [17], using a fixed-bowl mixer with meshing blades, linked a torque arm to a dynamometer to monitor the process. The amplitude of oscillation (torque range) and the mean torque increase from baseline were the parameters recorded. Torque showed a relation for the force required to shear the wet mass and provided an output for determining the wet mass strength. Integrating the torque–time curve yields the total energy into the system for a particular time period. Hancock defined the term, cumulative energy of mixing (CEM), and postulated its use as a means of scaling-up.

Vojnovic et al. [18] determined that peripheral speed of the impeller in a vertical high shear mixer was an important factor and adjusted this speed as a function of the diameter of the larger mixer. They found this to

### Low Shear Granulators



**Fig. 9** Schematic of a Zip-Zag machine. (Courtesy of Patterson-Kelley, Pittsburgh PA.)



**Fig. 10** Zig-Zag mixer—agglomerator. (Courtesy of Harsco Corp., East Stroudsburg PA.)

sed, there are some examples of adaptation of the batch, rotating Zig-Zag mixer (Figs. 9 and 10). g chamber connected to a series principles of fluid addition and disk ble to the Zig-Zag. The typical of the vessel.

somewhat by raising or lowering horizontal. Residence times are in ations. Two types of granulation material is in the high-speed—the powder in a manner similar material travels into the tumbling umbling section splits its load in material to proceed forward while action tends to smooth out any

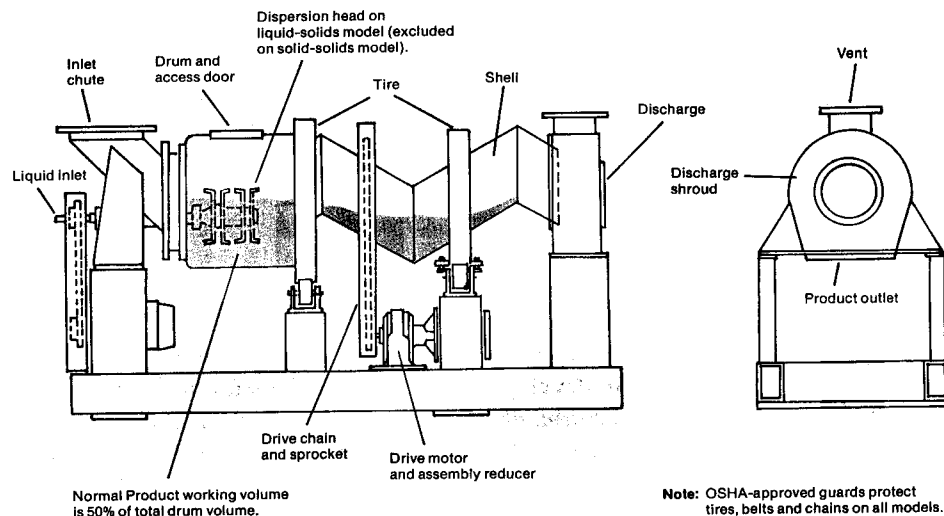
sed on constant residence times. a residence time of 3–5 min can e of producing 30,000 kg/h.

menting a granulation process is lved and the poorly understood cale-up in the realm of trial and owl mixer with meshing blades, nitor the process. The amplitude torque increase from baseline wned a relation for the force rel an output for determining the me curve yields the total energy Hancock defined the term, cu- stulated its use as a means of

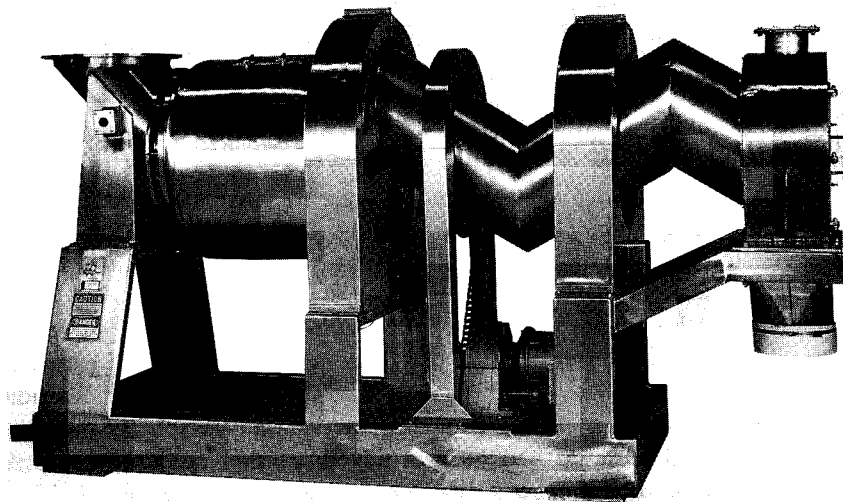
peripheral speed of the impeller portant factor and adjusted this arger mixer. They found this to

## Low Shear Granulators

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**Fig. 9** Schematic of a Zip-Zag, which is an example of a continuous granulating machine. (Courtesy of Patterson-Kelley Co., Division of Harsco Corp., East Stroudsburg PA.)



**Fig. 10** Zig-Zag mixer—agglomerator. (Courtesy of Patterson-Kelley Co., Division of Harsco Corp., East Stroudsburg PA.)

be an adequate scale-up method despite a geometric dissimilarity in the two mixers they studied.

Further work on the rheologic character of the wet mass and the effect on scale-up was performed by York in a high shear mixer-granulator [19]. It was theorized that the power number-Reynolds number relation used in scale-up of fluid mixing impeller systems could be applicable to the granulation mechanism in a high shear mixer. To analyze the relation, appropriate machine parameters needed to be measured, as did the density and viscosity value of the wet mass. Mixer torque rheometry (MTR) was used to determine wet mass viscosity, and this yielded a pseudo-Reynolds number with the units of torque. It is interesting to note that some unit operations textbooks show similar logic in developing scale-up equations for drying powder mixing [20]. Scaling-up the granulation process in a low shear granulator is a daunting task. Scale-up equations are usually proprietary to the machine manufacturers and little is written about them in the literature. The equations have a sound basis in science, but are ameliorated by constants and factors that take into consideration empirical feedback and intuition concerning the machine parameters.

Most commonly, a energy/volume ratio is established in the smaller vessel. This ratio is emulated in the larger vessel, with the appropriate consideration for the added mass and the larger motor, to yield an estimated scale-up time.

Scarpone et al. [21] studied a change in granulation technology from a high shear mixing bowl to a V-shaped granulator. Developmental work was done in an  $0.056\text{-m}^3$  ( $2\text{-ft}^3$ ) vessel and the ultimate production in a  $2.83\text{-m}^3$  ( $100\text{-ft}^3$ ) vessel. Scale-up based on the manufacturer's recommendation was not exact and required some fine-tuning before the process was established in the larger vessel.

This study provides a more detailed look at some of the hazards encountered in scaling-up. The initial trial in the  $2.83\text{-m}^3$  ( $100\text{-ft}^3$ ) production vessel failed to provide an adequate granulation. The main reason for failure was that the scale-up trial lacked the active ingredient and contained only excipient. This highlights the necessity of maintaining as much constancy as possible, both with formulation and process variables. Additional tests with the active ingredient, which happened to be 80% of the formulation, were much closer to the results gained in the smaller vessel. By the third trial, a successful scale-up had been achieved. Further studies were conducted to evaluate the influence of changes in the physical characteristics of the active ingredient: Density changes had an influence on the liquid needed. The researchers were able to use their knowledge from the scale-up to effect another scale-up on a different product.

## Low Shear Granulators

Ulveri et al. [22] also a laboratory vessel was a  $0.056\text{-m}^3$  ( $2\text{-ft}^3$ ). They found that the scale-up was 10:2 times over the direct 10:2 scale-up, and that the granulation mechanism was different.

Suitably, an article by [23] discussing granulation scale-up.

## V. ENDPOINT DETERMINATION

The rapidity by which granulation can be determined is a difficult problem. Growth of granules is modeled by the differential equations. The model used an infrared moisture sensor to monitor the moisture in a PID feedback loop. The pump until a suitable size was reached. The power consumption curve is used to determine the phases that were dependent on the granulation workers [3], working in a granulation plant. The determination using specific torque sensor between the slip ring torque sensor between the motor and the observed five phases in the granulation process should be considered for granulation. The monitoring of current is used for the determination; however, a granulation research by a V-shaped granulator. Additional current was needed when compared with an granulation throughout liquid addition. The current then decreased. The current then distributed within the powder through the bed. Finally, the dry powder reading and the mix cycle.

## VI. SUMMARY

Low shear granulators offer a number of advantages. They allow formulators to compare these vessels, compared with

geometric dissimilarity in the two  
ter of the wet mass and the effect  
high shear mixer-granulator [19].  
Reynolds number relation used in  
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Ulveri et al. [22] also attempted scale-up in a V-shaped granulator. The laboratory vessel was a 0.056-m<sup>3</sup> (2-ft<sup>3</sup>) model and the scale-up vessel was 0.283-m<sup>3</sup> (10-ft<sup>3</sup>). They found it was necessary to increase the batch size 1.2 times over the direct 10:2 ratio, that total liquid needed was 82% of direct scale-up, and that the granules were slightly larger in the scale-up vessel.

Suitably, an article by Ennis et al. [23] highlighted the fact that understanding granulation scale-up is a needed growth area for further research.

## V. ENDPOINT DETERMINATION AND CONTROL

The rapidity by which granulation proceeds makes endpoint determination a difficult problem. Growth behavior is nonlinear, preventing easy solutions to the differential equations describing the process [24]. Watano et al. [10] used an infrared moisture sensor to continuously monitor moisture through a PID feedback loop. The current was used to control the liquid addition pump until a suitable size was achieved. Leuenberger et al. [25] plotted the power consumption curve in a planetary mixer and observed five distinct phases that were dependent on the amount of liquid added. Zoglio and co-workers [3], working in a ribbon blender, postulated a potential endpoint determination using specific pore surface area. Ghanta et al. [7] installed a slip ring torque sensor between the Hobart mixer agitator and motor and observed five phases in the torque profile. This profile was repeatable and should be considered for granulation endpoint control in this style mixer. The monitoring of current is acknowledged as a poor method of endpoint determination; however, a similar five-phase curve was noted in internal research by a V-shaped granulator manufacturer. Approximately 0.6-amps—additional current was needed for the bar to travel through the dry powder, when compared with an empty blender. Amperage increased gradually throughout liquid addition and peaked a few seconds after liquid addition ceased. The current then dropped slightly as the binder became more fully distributed within the powder bed, and the bar had an easier time traveling through the bed. Finally, the current settled at a value of 0.2–0.3 amp above the dry powder reading and remained there, even through an extended post-mix cycle.

## VI. SUMMARY

Low shear granulators offer a middle ground solution for many of the problems formulators may encounter. Much denser granules may be produced in these vessels, compared with a fluid bed device, yet the energy expended is

not as great as that found in a high shear machine. Many of the low shear granulators are extremely adaptable devices capable of mixing the formula constituents before granulating, and some even dry the materials after granulation is complete. Ample opportunity is available in these granulators for adjustments: energy input may be altered with variable speed drives; droplet size may be changed through judicious selection of spray heads; and various agitating bar designs may be selected. As with many other granulating devices, scale-up and endpoint detection in low shear granulators remains poorly defined. A trial and error procedure is often the only method to determine endpoint and scale-up.

## REFERENCES

- ATI Nouh. The effect of variations in concentration and type of binder on the physical characteristics of sulfadiazine tablets and granulations prepared by wet and fluidised-bed granulation method. *Pharm Ind* 48(6):670, 1986.
- AY Gore, DW McFarland, NH Batuyios. Fluid-bed granulation: factors affecting the process in laboratory development and production scale-up. *Pharm Technol* Sept, 1985, pp. 114-122.
- MA Zoglio, HE Huber, G Koehne, PL Chan, JT Carstensen. Physical aspects of wet granulation II: factors involved in prolonged and excessive mixing. *J Pharm Sci* 65:1205, 1976.
- R Murry. *J Pharm Sci* 57:1776-1779, 1968.
- S Ghali, AM Contractor, AD Mankad, RE O'Connor, JB Schwartz, DE Auslander, WM Grim. A high-speed mixer for continuous wet granulation. *Pharm Technol* 14:60, 1990.
- JP Remon, JB Schwartz. Effect of raw materials and processing on the quality of granules prepared from microcrystalline cellulose-lactose mixtures. *Drug Dev Ind Pharm* 13:1, 1987.
- SR Ghanta, R Srinivas, CT Rhodes. Use of mixer torque measurements as an aid to optimizing wet granulation process. *Drug Dev Ind Pharm* 10:305-311, 1984.
- JH Day & Co. News bulletin: monitoring particle density, moisture content, particle size, and process weight. Cincinnati, Ohio, 1983.
- T Schaefer. Equipment for wet granulation. *Acta Pharm Suec* 25:205, 1988.
- S Watano, K Terashita, K Miyanami. Determination of end-point with a complex granulation applying infrared moisture sensor. *Chem Pharm Bull* 39:1013, 1991.
- TS Chirkot. Unpublished results.
- A Stamm, L Paris. Influence of technological factors on the optimal granulation liquid requirement measured by powder consumption. *Drug Dev Ind Pharm* 11:333, 1985.
- MJ Cliff. Granulation en granulators: Part I. *Pharm*
- D Lipps, AM Sakr. Cha using response surface m 83:937, 1994.
- JJ Fischer. Liquid-solids
- NO Lindberg, C Jonsson. high-speed mixer, Diosna
- C Hancock, P York, RC using a mixer torque rheo 76:239, 1991.
- D Vojnovic, M Moneghin of several response varia 19:1479, 1993.
- P York. Granulation using Meeting, Urbana IL, 1993
- WL McCabe, JC Smith, F 4th ed. New York: McGra
- AJ Scarpone, UG Dalvi, A cu ft solids processor. *Pha*
- M Ulveri, M Eli, R Bianco ulation technology. *Proces*
- BJ Ennis, J Green, R Dav p. 32, Apr, 1994.
- R Oliver, LJ Ford. The r nology. *Proceedings of T* lando FL, 1987, pp. 1-32
- H Leuenberger, HP Bier, ment in the conventional

machine. Many of the low shear granulators are capable of mixing the formula even dry the materials after granulation. Available in these granulators for granulation with variable speed drives; droplet formation of spray heads; and various other features with many other granulating devices. The use of low shear granulators remains the only method to

concentration and type of binder on the granules and granulations prepared by wet granulation. *Pharm Ind* 48(6):670, 1986.

Fluid-bed granulation: factors affecting granulation and production scale-up. *Pharm*

an, JT Carstensen. Physical aspects of granulation: prolonged and excessive mixing. *J*

8. O'Connor, JB Schwartz, DE Ausman. Continuous wet granulation. *Pharm*

materials and processing on the quality of granulations of cellulose-lactose mixtures. *Drug*

of mixer torque measurements as an indicator of granulation. *Drug Dev Ind Pharm* 10:305-311,

particle density, moisture content, and granulation. *Pharm Ind*, Ohio, 1983.

Acta Pharm Suec 25:205, 1988. Determination of end-point with a computerized sensor. *Chem Pharm Bull* 39:1013,

al factors on the optimal granulation process and consumption. *Drug Dev Ind Pharm*

13. MJ Cliff. Granulation end point and automated process control of mixer-granulators: Part I. *Pharm Technol* 14:112, 1990.
14. D Lipps, AM Sakr. Characterization of wet granulation process parameters using response surface methodology. 1. Top-spray fluidized bed. *J Pharm Sci* 83:937, 1994.
15. JJ Fischer. Liquid-solids blending. *Chem Eng* p. 3, Feb. 5, 1962.
16. NO Lindberg, C Jonsson. The granulation of lactose and starch in a recording high-speed mixer, Diosna P25. *Drug Dev Ind Pharm* 11:387, 1985.
17. C Hancock, P York, RC Rowe, MD Parker. Characterization of wet masses using a mixer torque rheometer: 1. Effect of instrument geometry. *Int J Pharm* 76:239, 1991.
18. D Vojnovic, M Moneghini, F Rubessa, A Zanchetta. Simultaneous optimization of several response variables in a granulation process. *Drug Dev Ind Pharm* 19:1479, 1993.
19. P York. Granulation using mechanical agitation. *Proceedings of IFPRI Annual Meeting*, Urbana IL, 1995.
20. WL McCabe, JC Smith, P Harriot. *Units Operations of Chemical Engineering*. 4th ed. New York: McGraw-Hill, 1985, p. 846.
21. AJ Scarpone, UG Dalvi, AE Delorimier. Preparing tablet granulations in a 100 cu ft solids processor. *Pharm Technol* 10:44, 1986.
22. M Ulveri, M Eli, R Bianchini. Patterson Kelley Solids Processor, a wet granulation technology. *Process Development*, unpublished research.
23. BJ Ennis, J Green, R Davies. The legacy of neglect in the US. *Chem Eng Prog* p. 32, Apr, 1994.
24. R Oliver, LJ Ford. The role of agglomeration in chemical and process technology. *Proceedings of The Institute for Briquetting and Agglomeration*, Orlando FL, 1987, pp. 1-32.
25. H Leuenberger, HP Bier, HB Sucker. Theory of the granulating liquid requirement in the conventional granulation process. *Pharm Technol* 11:76, 1986.

# 9

## Batch Fluid Bed Granulation

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## I. INTRODUCTION

*Fluidization* is the operation by which fine solids are transformed into a fluid-like state through contact with a gas. At certain gas velocities, the fluid will support the particles, giving them freedom of mobility without entrainment. Such a fluidized bed resembles a vigorously boiling fluid, with solid particles undergoing extremely turbulent motion, which increases with gas velocity.

*Fluidized bed granulation* is a process by which granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. This process is sometimes classified as the one-pot system. The fluid bed granulation process has received considerable attention within the pharmaceutical industry; however, other process industries, such as food, agrochemical, dyestuffs, and other chemical industries, have adopted fluid bed granulation process to address particle agglomeration, dust containment, and material handling. The fluidization technique, as it is known today, began in 1942, with the work of the Standard Oil Company (now known as Exxon, in the United States) and M. W. Kellogg Company, in an effort to produce the first catalytic cracking plant on a commercial scale [1].

Fluid bed processing of pharmaceuticals was first reported by Wurster, when he used the air suspension technique to coat tablets [2–3]. In 1960 he

reported on granulating and for the preparation of comp In 1964 Scott et al. [4] an design considerations of th proach and employing mas this application to the 30-k and continuous operation. P temperature, and liquid flow reported the processing det in one continuous step. Wol of the various fluid bed co the fluidized bed and trad indicated that the material more free-flowing, and had produced stronger and faste cessed by conventional wet [9], Pietch [10], and a serie Pharmaceutical Industry” [ fundamental aspects of the The fluidized bed was used efficiently in the early days glomerating, pelletizing, and air suspension coating. Bec tiprocessor fluid bed units.

## II. SYSTEM DESCRIPTION

A *fluid bed processor* is a of process air, directing it have the same air (usually product. Figure 1 shows a nents. These components a viewed.

At the downstream er or fan is situated to draw t provides negative pressure material loading, maintain s out the process under good of which will be discussed

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reported on granulating and drying a pharmaceutical granulation, suitable for the preparation of compressed tablets, using the air suspension technique. In 1964 Scott et al. [4] and Rankell et al. [5] reported on the theory and design considerations of the process using a fundamental engineering approach and employing mass and thermal energy balances. They expanded this application to the 30-kg-capacity pilot model designed for both batch and continuous operation. Process variables, such as airflow rate, process air temperature, and liquid flow rate, were studied. Contini and Atasoy [6] later reported the processing details and advantages of the fluidized bed process in one continuous step. Wolf [7] discussed the essential construction features of the various fluid bed components, and Liske and Mobus [8] compared the fluidized bed and traditional granulation process. The overall results indicated that the material processed by the fluid bed granulator was finer, more free-flowing, and had homogeneous granules which, after compression, produced stronger and faster disintegration of tablets than the materials processed by conventional wet granulation. Reviews by Sherrington and Oliver [9], Pietch [10], and a series published on the topic of "Fluidization in the Pharmaceutical Industry" [11-17] provide an in-depth background on the fundamental aspects of the fluidized bed and other granulating technologies. The fluidized bed was used only for drying the pharmaceutical granulation efficiently in the early days, but now is employed routinely for drying, agglomerating, pelletizing, and producing modified-release dosage forms using air suspension coating. Because of this, these units are normally called multiprocessor fluid bed units.

## II. SYSTEM DESCRIPTION

A *fluid bed processor* is a system of unit operations involving the heating of process air, directing it through the material to be processed, and then have the same air (usually laden with moisture) exit the unit void of the product. Figure 1 shows a typical fluid bed processor with all the components. These components and their usefulness for granulation will be reviewed.

At the downstream end of the fluid bed processor, an exhaust blower or fan is situated to draw the air through the entire unit. This arrangement provides negative pressure in the fluid bed, which is necessary to facilitate material loading, maintain safe operation, prevent material escape, and carry out the process under good manufacturing practices (GMP) guidelines, all of which will be discussed later in the chapter.

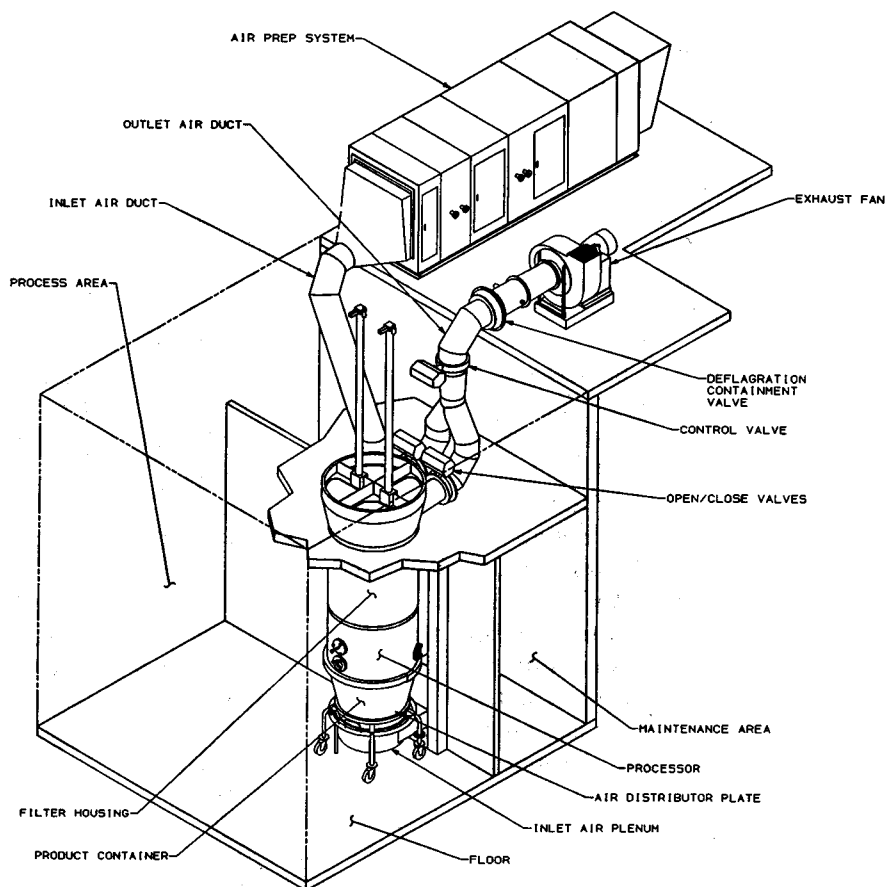


Fig. 1 Fluid bed processor installation with all components.

### A. Air-Handling Unit

A typical air preparation system includes sections for air filtering, air heating, air cooling, and humidity removal. Generally, outside air is used as the fluidizing medium in a fluid bed processor. For the air to be used for pharmaceutical products, it must be free of dust and contaminants. This is achieved by placing coarse dust filters (30–85%) in the air-handling unit (AHU). Figure 2 shows the typical air-handling unit.

After the filters, distinct heating or cooling sections are installed in the air handler, depending on the geographic location of the plant. In an ex-

### Batch Fluid Bed Granulation

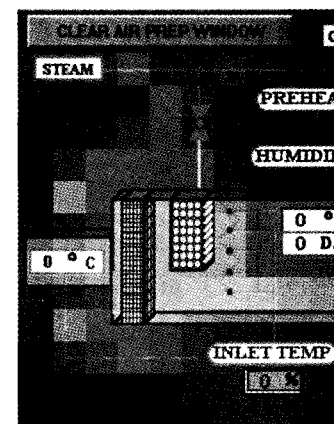
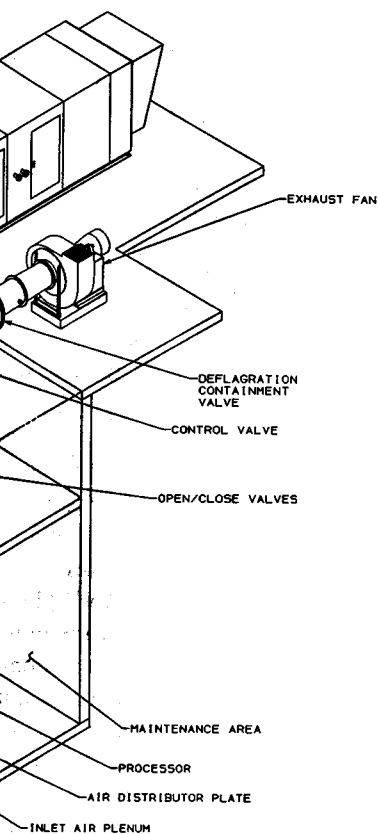


Fig. 2 Air-handling unit. (Continued)

tremely cold climate, where maintaining uniform dew point is placed ahead of the cooling section should aim to achieve after wet bulb. If the unit is located in a removal section is employed, it is extremely important in regions with a wide range. In summer, where the incoming process air is hot, In some regions, rehumidification is required for months. A steam injector is used to lower the process air dew point and the shorter the process air, an inlet air dew point of 10°C facilitate uniform fluidization. If required, a bypass loop can be installed to allow the required process air to pass through the system ducts before the air is conditioned. After the air leaves the AHU, it is finally heated to 100°C and passed through a high-efficiency filter with 99.90–99.99% capacity. As the air is heated, it is supported by the inlet duct. The air then passes through the lower plenum.



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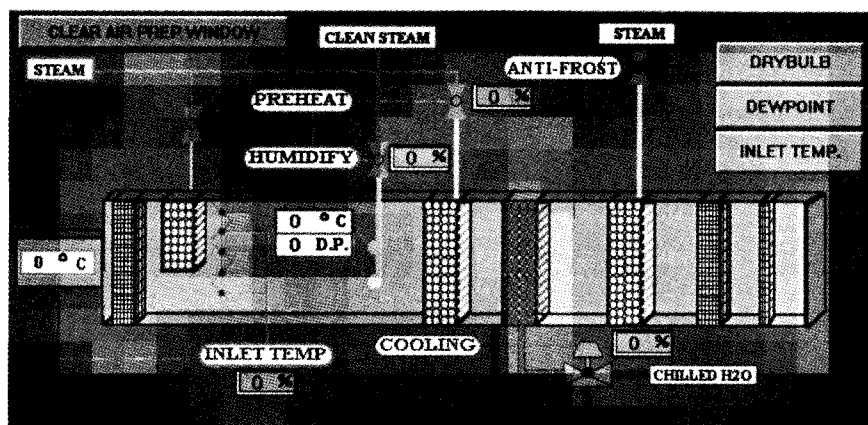


Fig. 2 Air-handling unit. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

tremely cold climate, where cooling coils (needed in summer months for maintaining uniform dew point) can freeze in winter, a preheating section is placed ahead of the cooling coils. A typical range for the air that one should aim to achieve after pretreatment is 15–30°C dry bulb and 3–5°C wet bulb. If the unit is located in a tropical or humid climate, the humidity removal section is employed first. The dehumidification of the air is extremely important in regions where the outside air moisture varies over a wide range. In summer, when the outside humidity is high, dehumidification of the incoming process air is required to maintain its specific dew point. In some regions, rehumidification may be necessary during the winter months. A steam injector is used for rehumidifying the dry air. Generally, the lower the process air dew point, the higher the affinity to entrain moisture and the shorter the process time. When granulating extremely fine powders, an inlet air dew point of 15°C is beneficial to reduce static charges and facilitate uniform fluidization. In many processes when preheating is required, a bypass loop can be used for preconditioning the air. This loop allows the required process temperature and humidity to be attained within the system ducts before the product is subjected to fluidization. After the conditioned air leaves the humidification–dehumidification section of the AHU, it is finally heated to the desired process air temperature and then passed through a high-efficiency particulate air (HEPA) filter of about 99.90–99.99% capacity. As the process air is treated and filtered, it is transported by the inlet duct. The air is thus brought into the process vessel through the lower plenum.

## B. Product Container and Air Distributor

With the air at the desired humidity and temperature, it is ready to be passed through the bed of solids. Figure 3 shows typical product container with the air distributor.

The air must be introduced evenly at the bottom of the product container through an inlet air plenum. Proper airflow in the inlet air plenum is critical to ensure that equal airflow velocities occur at every point on the air distributor plate. If the air is not properly distributed before it reaches the bottom of the container, uneven fluidization can occur.

To properly fluidize and mix material in the container, a correct choice of the container and air distributor must be made. The container volume should be chosen such that the bowl is filled to at least 35–40%, but to no more than 90%, of its total volume. Correct choice of the air distributor is important. These distributors are made of stainless steel and are available with a 2–30% open area. Typically, the distributor should be chosen so that the pressure drop across the product bed and air distributor is 200–300 mm wc (water column). A fine screen of 60–325 mesh normally covers the air distributor and retains the product in the container. This type of sandwiched construction has been used for the last 30 years in the fluid bed processors.

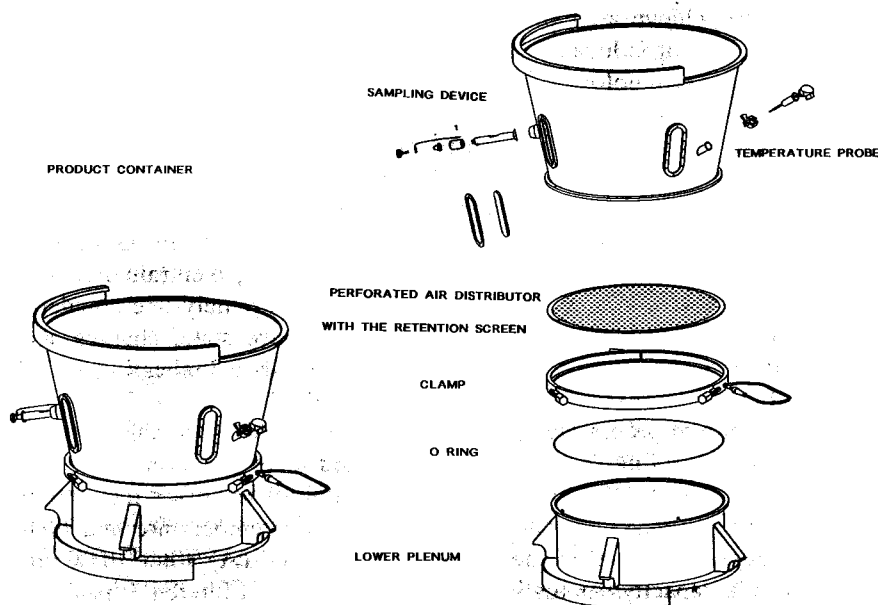


Fig. 3 Product container with air distributor.

## Batch Fluid Bed Granulation

The classic air distributor shown in Fig. 3.

Keeping the screen and partially to address the cleaning processing, a new overlap design [101]. These new overlap design screen and perform dual function retainer. Other advantages include clean-in-place (cip), controlled discharge the processed product.

## C. Spray Nozzle

A *spray* is a zone of liquid disrupted up a liquid into a multitude of droplets. The purpose of spraying is to increase the surface area over the product area. The solution (one fluid) is atomized. The commonly used nozzle for this purpose are available as a single-port or multiport. If single-port nozzles are adequate for a batch process, a multiport (either three or four) are air-atomized, the spray of compressed air (gas) expands to the pressure at the nozzle to that of the Joule–Thomson effect, and the liquid forms into discrete drops. During this phase, the surface area usually increases as the drops are being formed, until they become particles. During this phase, the surface area of the drops decreases. The energy of the surface tension and the nozzle pressure are used to subdivide 1 g of water into 100,000 droplets. The atomize the binder liquid in a pattern and spray angle is a function of the nozzle design.

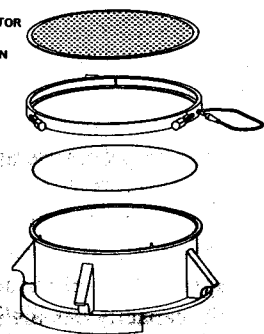
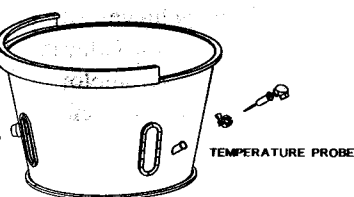
The binder solution is pumped through a lance and tubing (see Fig. 5) to the nozzle. The nozzle is commonly used to pump the binder solution. The nozzle needle prevents the binder from being stopped. Nozzle port openings are most common and are

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ears in the fluid bed processors.



The classic air distributor with the fine, product-retaining screen is also shown in Fig. 3.

Keeping the screen and air distributors clean has been challenging. Partially to address the cleaning problems and partially to provide efficient processing, a new overlap gill plate (Fig. 4a and b) was introduced in 1990 [101]. These new overlap gill air distributors eliminate the need for a fine screen and perform dual functions as the efficient air distributor and product retainer. Other advantages claimed by the manufacturer are validatable clean-in-place (cip), controlled fluidization and directional flow of air to discharge the processed product from the container.

### C. Spray Nozzle

A *spray* is a zone of liquid drops in a gas, and *spraying* is the act of breaking up a liquid into a multitude of these droplets. The general purpose of spraying is to increase the surface area of a given mass of liquid to disperse it over the product area. The two-fluid (binary) nozzle in which the binder solution (one fluid) is atomized by compressed air (second fluid) is the most commonly used nozzle for the fluid bed granulation (Fig. 5a). These nozzles are available as a single-port or multiport design. Generally, the single-port nozzles are adequate for a batch of up to 100 kg, but for larger-sized batches a multiport (either three or six port) nozzle is required. When these nozzles are air-atomized, the spray undergoes three distinct phases. In the first, the compressed air (gas) expands, essentially adiabatically, from the high pressure at the nozzle to that of the fluid bed chamber. The gas undergoes a Joule–Thomson effect, and its temperature falls. In the second, the liquid forms into discrete drops. During this atomization, the liquid's specific surface area usually increases 1000 times. In the third, the drops travel, after being formed, until they become completely dry or impinge on the product particles. During this phase, the solvent evaporates, and the diameter of the drops decreases. The energy required to form a drop is the product of the surface tension and the new surface area. About 0.1 cal/g is needed to subdivide 1 g of water into 1- $\mu$ m droplets. The air pressure required to atomize the binder liquid is set by means of pressure regulator. The spray pattern and spray angle is adjusted by adjusting the air cap.

The binder solution is delivered to the nozzle port through a spray lance and tubing (see Fig. 5b). The peristaltic or positive displacement pump is commonly used to pump the binder solution. The pneumatically controlled nozzle needle prevents the binder liquid from dripping when the fluid flow is stopped. Nozzle port openings of between 0.8 and 2.8 mm in diameter are most common and are interchangeable.

#### D. Disengagement Area

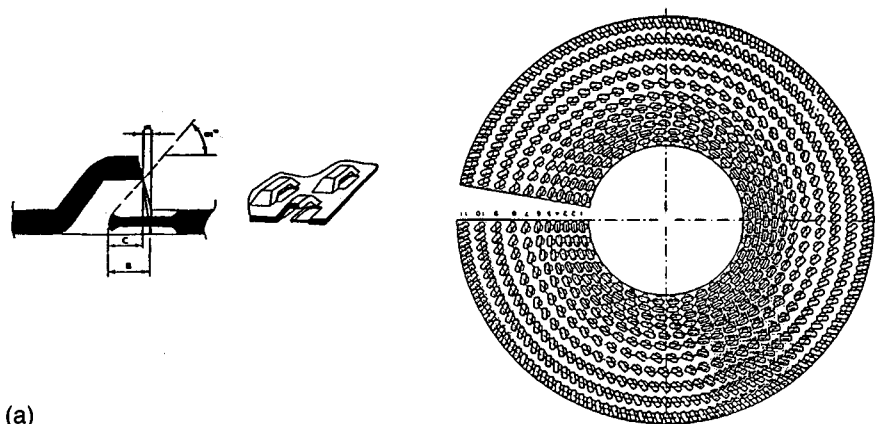
Once the air leaves the product bed, the air stream; two zones are formed: the disengagement area and the exhaust area. In the disengagement area, the particles lose momentum and the process air is highest at the center of the sidewalls. A process air stream is exhausted. The process air is exhausted. The process air can be constructed out of nylon, fluoropolyethylene (PTFE)-lined, or stainless steel. Cartridge charges from the product particles are recommended. Cartridge charges are recommended in the industry in the 1980s [102]. The air stream is able for cip have been introduced during the granulation process. The pressure blowback system. Fluid bed processors.

#### E. Exhaust Blower or Fan

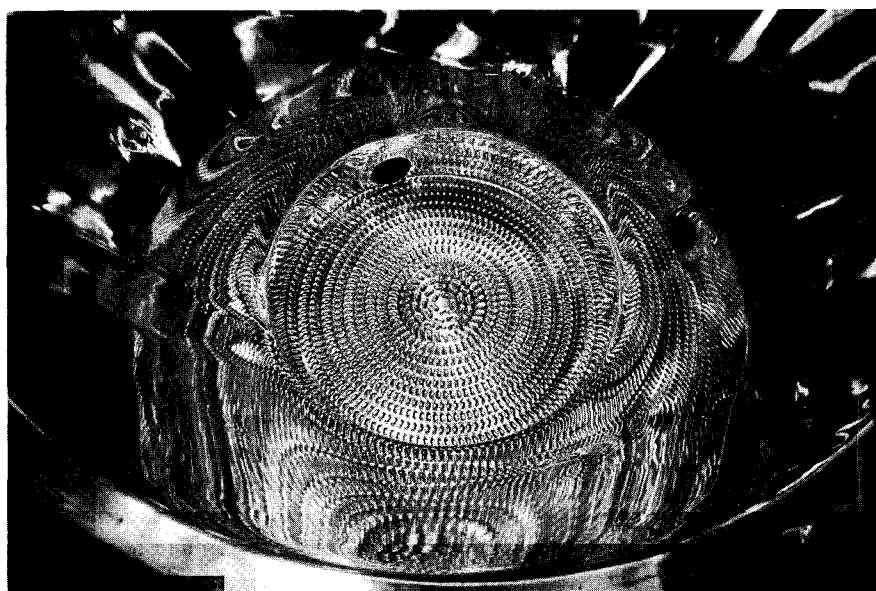
Once the air leaves the exhaust, the outlet side of the system is higher than the surrounding atmosphere. A damper installed just ahead of the fan is normally done by the manufacturer of the system. Fan size is determined by the pressure drop created by all the components in the system. The product, at the highest density.

#### F. Control System

Fluid bed granulation processes are controlled by control devices, or using state-of-the-art computers. The electronic control system is able to handle multiple batches according to the process conditions. The process conditions are rapidly, and it will continue to take place and as the cost of

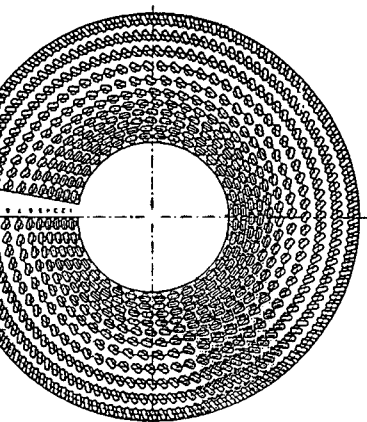


(a)



(b)

**Fig. 4** (a) Schematic of a overlap gill air distributor; (b) Container with the overlap air distributor and side discharge opening. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)



utor; (b) Container with the overlap  
tesy of Niro Inc., Aeromatic-Fielder

#### D. Disengagement Area and Process Filters

Once the air leaves the product bed, fine particles need to be separated from the air stream; two zones are used in the fluid bed for this process: the disengagement area and the exhaust filters. In the disengagement area, larger particles lose momentum and fall back into the bed. The velocity of the process air is highest at the center of the processor and approaches zero at the sidewalls. A process air filter system removes the particles from the exhaust air. The process air is filtered by using bags or cartridges. The bags can be constructed out of nylon-, polyester-, polypropylene-, or polytetrafluoroethylene (PTFE)-lined materials. To dissipate the potential static charges from the product particles, conductive fabrics are also available and are recommended. Cartridge filters lined with PTFE were introduced to the industry in the 1980s [102]. Recently cartridges made of stainless steel suitable for cip have been introduced [103]. These process filters are cleaned during the granulation process by mechanical means or by using a low-pressure blowback system. Figure 6 shows various filters used in the fluid bed processors.

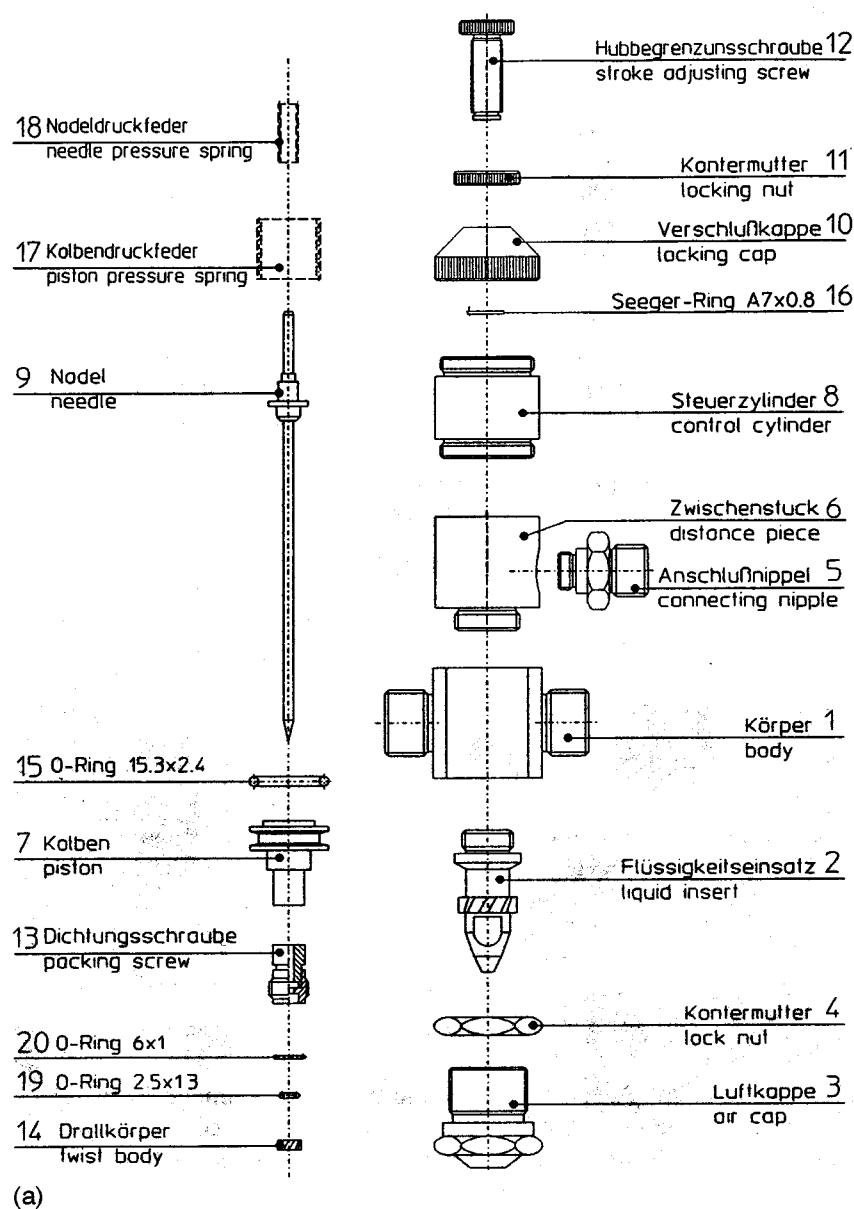
#### E. Exhaust Blower or Fan

Once the air leaves the exhaust filters, it travels to the fan. The fan is on the outlet side of the system, which keeps the system at a lower pressure than the surrounding atmosphere. The airflow is controlled by a valve or damper installed just ahead or after the fan. The selection of the fan is normally done by the manufacturer, based on the layout and complexity of the system. Fan size is determined by calculating the pressure drop ( $\Delta P$ ) created by all the components that make up the fluid bed processor, including the product, at the highest design airflow volume.

#### F. Control System

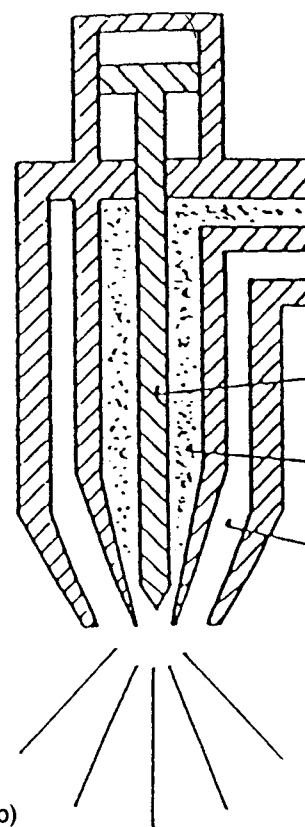
Fluid bed granulation processes can be controlled by pneumatic analog control devices, or using state-of-the-art, programmable logic controllers (PLC) or computers. The electronic-based control system offers not only reproducible batches according to the recipe, but also a complete record and printout of all the process conditions. Process control technology has changed very rapidly, and it will continue to change as advances in computer technology take place and as the cost of control systems fall.





(a)

**Fig. 5** (a) Schematic nozzle showing different parts; (b) Schematic of a two-fluid nozzle showing liquid and air pathways. (Courtesy of Gustav Schlick GmbH & Co., Germany.)



(b)

**Fig. 5** Continued

### G. Solution Delivery System

A peristaltic pump capable of high flow rate is desirable. The liquid is delivered through the tubing and atomized by the processor.

### III. FLUIDIZATION THEORY

A fluidized bed is a bed of solid particles through which a fluid is passed upward through the particles. This velocity, according to the minimum fluidizing velocity,

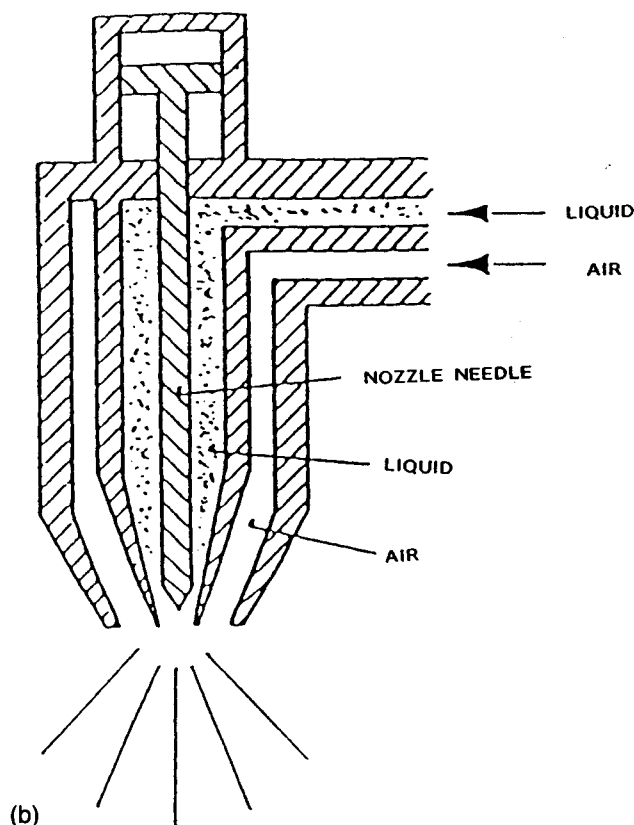
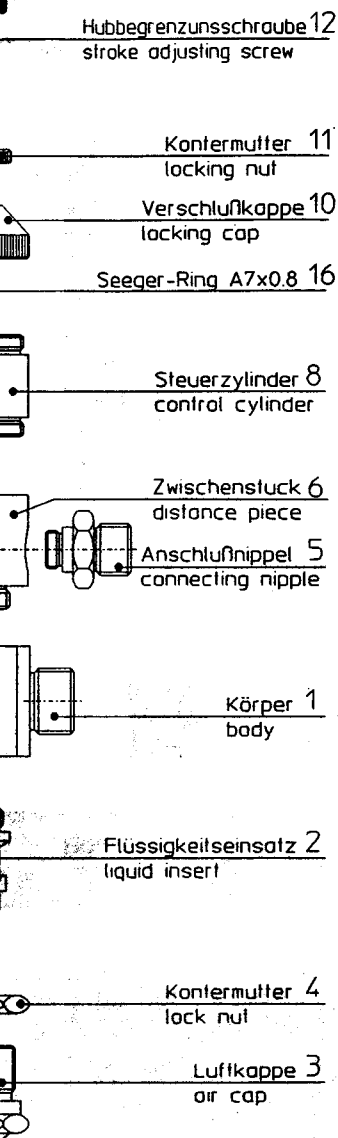


Fig. 5 Continued

### G. Solution Delivery System

A peristaltic pump capable of delivering the binder solution at a controlled rate is desirable. The liquid is transported from the solution vessel through the tubing and atomized using a two-fluid (binary) nozzle in the fluid bed processor.

### III. FLUIDIZATION THEORY

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate fast enough to set them in motion. This velocity, according to Kulling and Simon [18], is higher than the incipient fluidizing velocity, but lower than the entrainment velocity. When

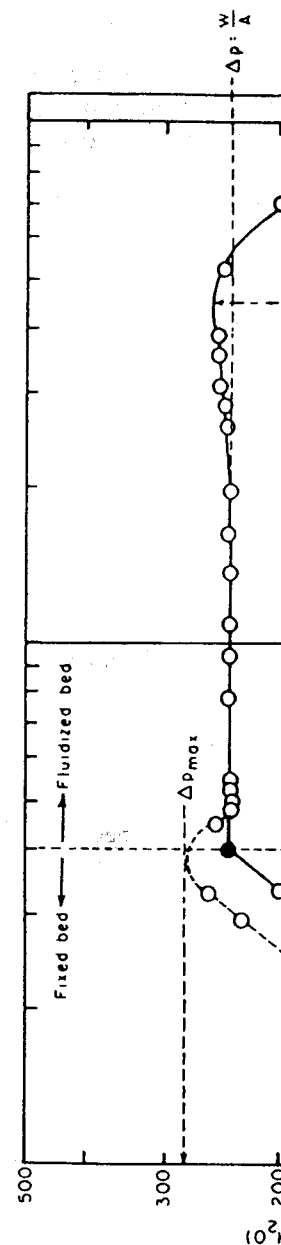


Fig. 6 Fluid bed process filters.

the rate of flow of gas increases, the pressure drop across the bed also increases until, at a certain rate of flow, the frictional drag on the particles equals the effective weight of the bed. These conditions, and the velocity of gas corresponding to them, are termed *incipient fluidization* and *incipient velocity*, respectively. The relation between the air velocity and the pressure drop is as shown in Figure 7 [19].

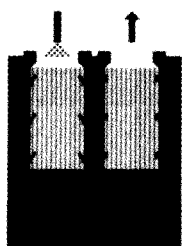
At low gas velocities, the bed of particles is practically a packed bed, and the pressure drop is proportional to the superficial velocity. As the gas velocity is increased, a point is reached at which the bed behavior changes from fixed particles to suspended particles. The superficial velocity required to first suspend the bed particles is known as the *minimum fluidization velocity* ( $u_{mf}$ ). The minimum fluidization velocity sets the lower limit of possible operating velocities, and the approximate pressure drop can be used to approximate pumping energy requirements. For agglomeration process in the fluid bed processor, the air velocity required is normally five to six times the minimum fluidization velocity. At the incipient point of fluidization, the pressure drop of the bed will be very close to the weight of the particles divided by the cross-sectional area of the bed ( $W/A$ ). For the normal gas fluidized bed, the density of the gas is much less than the density of the solids and the balance of forces can be shown as

$$\Delta P_{mf} = \frac{W}{A}$$





Back bag filter  
Filtering is carried out  
using compressed  
air to blow one segment of  
the filter at a time.



Cartridge filter  
Compressed air is used to  
blow back one cartridge  
at a time. This system  
can be supplied with CIP.

pressure drop across the bed also  
frictional drag on the particles  
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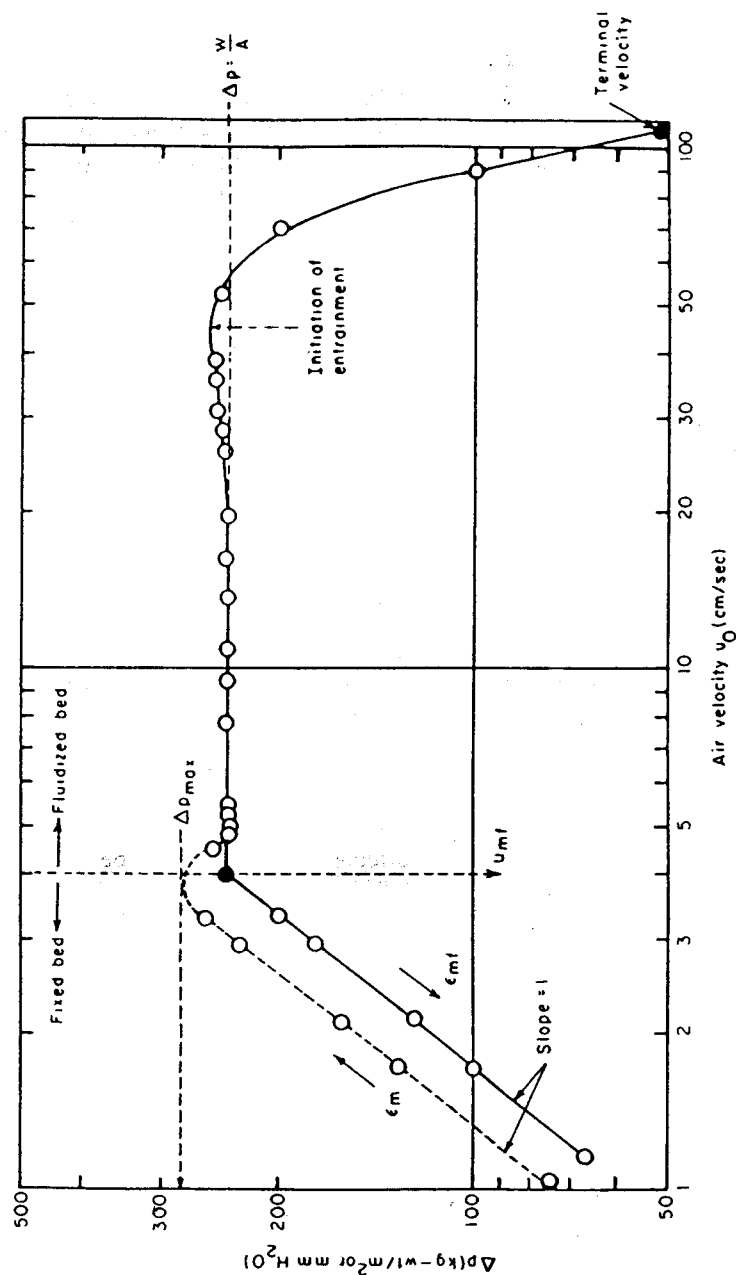


Fig. 7 Relation between the air velocity and pressure drop. (From Ref. 19.)

where

$$W = (1 - \epsilon_{mf}) \rho_p \left( \frac{g}{gc} \right)$$

where  $\Delta P$  = pressure drop,  $\epsilon_{mf}$  = minimum fluidization void fraction,  $A$  = cross-sectional area,  $W$  = weight of the particles,  $\rho_p$  = density of particles,  $g/gc$  = ratio of gravitational acceleration and gravitational conversion factor.

As the velocity of the gas is increased further, the bed continues to expand and its height increases with only slight increase in the pressure drop. As the velocity of the gas is further increased, the bed continues to expand and its height increases, whereas the concentration of particles per unit volume of the bed decreases. At a certain velocity of the fluidizing medium, known as *entrainment velocity*, particles are carried over by the gas. This phenomenon is called *entrainment*. When the volumetric concentration of solid particles is uniform throughout the bed at all the times, the fluidization is termed *particular*. When the concentration of solids is not uniform throughout the bed, and if the concentration keeps fluctuating with time, the fluidization is called *aggregative fluidization*.

A *slugging bed* is a fluid bed in which the gas bubbles occupy entire cross sections of the product container and divide the bed into layers.

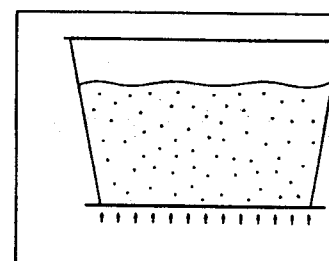
A *boiling bed* is a fluid bed in which the gas bubbles are approximately the same size as the solid particles.

A *channeling bed* is a fluid bed in which the gas forms channels in the bed through which most of the air passes.

A *spouting bed* is a fluid bed in which the gas forms a single opening through which some particles flow and fall on the outside.

Figure 8 shows various types of fluid beds [20].

The mechanisms by which air affects fluidization have been discussed by various researchers [13,21–25]. When the fluidizing velocity is greater than the incipient velocity, bubbles of air rise through the bed, causing mixing of particles. Mixing does not generally occur when the bed is fluidized at a very low or zero *excess* gas velocities, because insufficient bubbles are formed to cause bulk displacement of particles. It is the gas passing through the bed in the form of bubbles that determines the degree of mixing. The extent of mixing appears to vary with the particle size. Mixing of particles having a mean particle size smaller than approximately 150  $\mu\text{m}$  decreases as the mean size approaches zero. The different types of beds are formed, depending on the movement of bubbles through the bed. The pattern of movement of the gas phase in and out of bubbles depends on several factors, including minimum fluidization velocity and particle size. These movements affect heat transfer between air bubbles and particles. The air



An incipiently fluidized bed

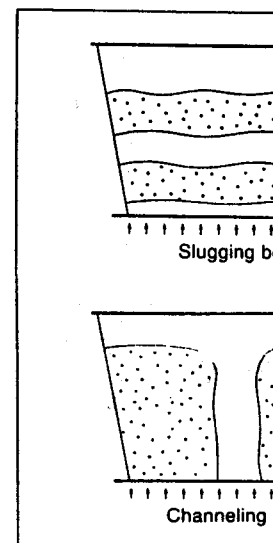
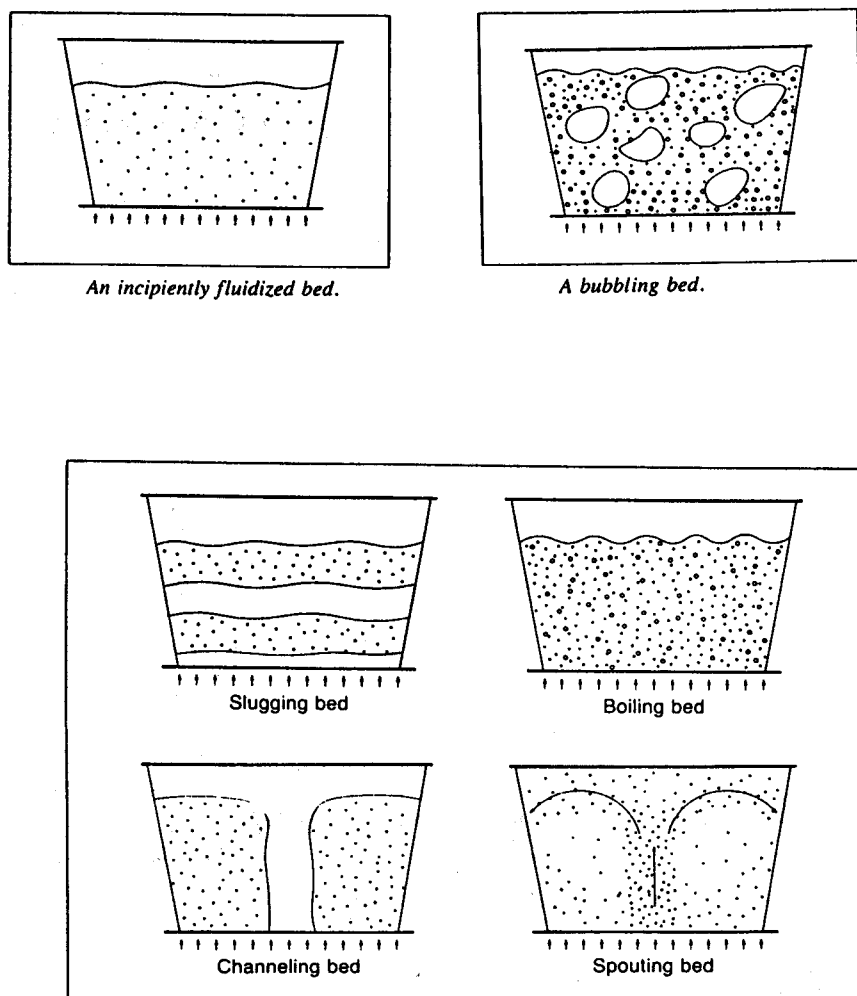


Fig. 8 Various types of fluid beds

distributor at the bottom of the bed provides a uniform distribution of gas, which leads to a uniform distribution of particle movement. The nature of particle movement, such as segregation, in the fluid bed depends on the extent of segregation can be minimized by increasing the fluidizing velocities and a high bo

s fluidization have been discussed. If the fluidizing velocity is greater, air rises through the bed, causing mixing to occur when the bed is fluidized. However, because insufficient bubbles are formed, mixing is poor. It is the gas passing through the bed that determines the degree of mixing. The degree of mixing depends on particle size. Mixing of particles with a diameter of approximately 150  $\mu\text{m}$  decreases as particle size increases. Different types of beds are formed, depending on the fluidizing velocity through the bed. The pattern of bubble formation depends on several factors, including fluidizing velocity and particle size. These factors determine the size of air bubbles and particles. The air



distributor at the bottom of the container has a controlling influence on the uniform distribution of gas, minimization of dead areas, and maximization of particle movement. The most common reason for mixing problems, such as segregation, in the fluid bed are the particle density differences. The extent of segregation can be partly controlled by maintaining high-fluidizing velocities and a high bowl height/bowl diameter ratio. There are stan-

standard air velocities for various processes that can be used as guidelines. The standard velocities are based on the cross-sectional area at the bottom of the product container.

This is calculated by using the following formula for calculating the air velocity:

$$\text{Velocity (m} \cdot \text{s}^{-1}) = \frac{\text{airflow (m}^3 \text{ h}^{-1}; \text{ CMH)}}{\text{area (m}^2) \times 3600}$$

where

$$\text{Airflow in cubic meters per hour (CMH)} = \text{airflow (CFM)} \times 1.696$$

Standard air velocities are based on the application. Low air velocities, such as  $0.8\text{--}1.4 \text{ m} \cdot \text{s}^{-1}$ , are required for drying. The velocities are higher during the early stages of drying because of the wet mass present in the bowl, but will be reduced when the product loses its moisture. The objective is to have good particle movement, but to keep the material out of filters. Particle movement and quick drying are important during the agglomeration process. Where airflow velocities are normally  $1.0\text{--}2.0 \text{ m} \cdot \text{s}^{-1}$ . An indication of good fluidization is a free downward flow of the granulation at the sight glass of the drying container. However, improper fluidization can also be detected by monitoring the outlet air temperature. Every product has a unique constant rate of drying in which the bed temperature remains relatively constant for a substantial length of time. Therefore, if the outlet temperature rises more rapidly than anticipated, it will indicate an improper fluidization; the process may have to be stopped, and manual or mechanical intervention may be required to assist the fluidization.

#### IV. PARTICLE AGGLOMERATION AND GRANULE GROWTH

*Agglomeration* can be defined as the size enlargement process, in which the starting material is fine particles and the final product is an aggregate in which primary particles can still be identified. The granules are held together with bonds formed by the binder used to agglomerate. Various mechanisms of granule formation have been described in the literature [26–28]. Chapter 2, on theory of granulation in this book, discusses the theory of granule growth. To summarize, three mechanisms for granule formation have been suggested by the researchers. These are

1. *Immobile liquids* form adhesional- and cohesion-bridging bonds. Thin adsorption layers are immobile and can contribute to the bonding of fine particles under certain circumstances.

2. *Mobile liquids* in v
3. *Solid bridges* form during drying.

The type of bonds for described by Newitt and Corn capillary, and (d) droplet, wh of the fluid bed granulated p shear granulation- or spray c lation process, the particles omized liquid is sprayed on particles to form an agglom the physicochemical charact ated, and on the process par enow [30] have reported a d bed, when the bed particles Atomized liquid from the no long as there is an adequate particles on impact, form a circulates throughout the ren ticles together. The strength stay as agglomerates. These forces and, in turn, depend o arise from movement of the and are related to the excess

If the binding forces a wet state or in the dry state wetted bed or production o able balance of forces is pre of which can be controlled. mechanism in the fluid be electron microscope [32]. F can take and their consequ

The mechanism of for gresses primarily through th

1. Nucleation
2. Transition
3. Ball growth

Figure 10 shows the growt the beginning of the spray held together by liquid brid

s that can be used as guidelines. cross-sectional area at the bottom

owing formula for calculating the

CMH)  
3600

CMH) = airflow (CFM)  $\times$  1.696

the application. Low air velocities, drying. The velocities are higher e of the wet mass present in the ct loses its moisture. The objective o keep the material out of filters. mportant during the agglomeration ally  $1.0\text{--}2.0\text{ m}\cdot\text{s}^{-1}$ . An indication low of the granulation at the sight improper fluidization can also be mperature. Every product has a he bed temperature remains rela-time. Therefore, if the outlet tem- ted, it will indicate an improperopped, and manual or mechanical fluidization.

## ND GRANULE

enlargement process, in which the final product is an aggregate in ed. The granules are held together agglomerate. Various mechanisms in the literature [26–28]. Chapter discusses the theory of granule for granule formation have been

l- and cohesional-bridging bonds. mobile and can contribute to the certain circumstances.

2. *Mobile liquids* in which interfacial and capillary forces are present.
3. *Solid bridges* formed by crystallization of dissolved substances during drying.

The type of bonds formed approaches through four transition states, described by Newitt and Conway-Jones [26] as (a) pendular, (b) funicular, (c) capillary, and (d) droplet, which normally happens during spray drying. Most of the fluid bed granulated products require less particle wetting than a high shear granulation- or spray dryer-processed product. In the fluid bed granulation process, the particles are suspended in the hot airstream and the atomized liquid is sprayed on it. The degree of bonding between these primary particles to form an agglomerated granule, depends on the binder used, on the physicochemical characteristics of the primary particles being agglomerated, and on the process parameters. Schaefer et al. [29] and Smith and Nienow [30] have reported a description of the growth mechanisms in the fluid bed, when the bed particles are wetted by liquid droplets in the spray zone. Atomized liquid from the nozzle tends to spread over the particle surface, as long as there is an adequate wettability of the particle by the fluid [31]. Wet particles on impact, form a liquid bridge and solidify as the agglomerate circulates throughout the remainder of the bed. Solid bridges then hold particles together. The strength of the binder determines whether these particles stay as agglomerates. These binding forces should be larger than the breakup forces and, in turn, depend on the size of the solid bridge. The breakup forces arise from movement of the randomized particles colliding with each other and are related to the excess gas velocity and particle size.

If the binding forces are in excess of the breakup forces, either in the wet state or in the dry state, uncontrolled growth will proceed to an over-wetted bed or production of excessive fines, respectively. If a more reasonable balance of forces is present, controlled agglomeration will occur, growth of which can be controlled. Maroglou and Nienow present a granule growth mechanism in the fluid bed by the use of model materials and scanning electron microscope [32]. Figure 9 shows the various paths a liquid droplet can take and their consequences on the particle growth.

The mechanism of formation of a granule and subsequent growth progresses primarily through three stages.

1. Nucleation
2. Transition
3. Ball growth

Figure 10 shows the growth of the granule relative to the liquid added. In the beginning of the spraying stage, primary particles form nuclei and are held together by liquid bridges in a pendular state. The size of these nuclei



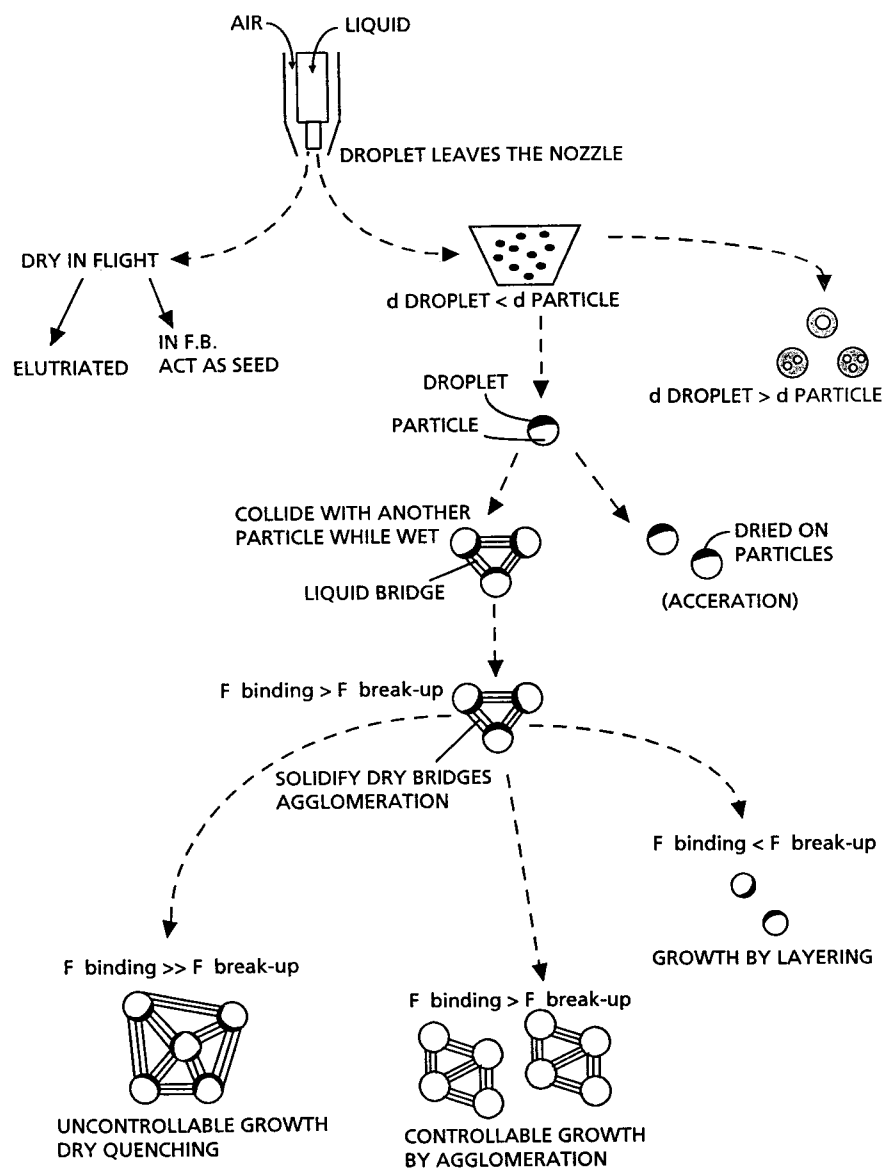
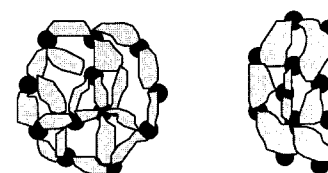


Fig. 9 Mechanism of granulation in fluid bed. (From Ref. 33.)



Pendular

Funicular

Fig. 10 States of liquid saturation

depends on the droplet size. As the droplet size continues, more and more of the liquid is added, moving the system from the pendular state to the funicular state.

The uniqueness of the fluid bed granulation process lies in the liquid addition and drying occurring simultaneously. When the granulation liquid is added, the particles are wetted and form a network of very porous agglomerates. The drying is controlled solely by the capillary forces. It is important that the granulation time is relatively large compared with the drying time.

Drying a wet product in a fluid bed during the granulation process it becomes a fluid bed drying process.

## V. FLUID BED DRYING

Drying is usually understood as a process involving heat and mass transfer. In fluid bed drying, liquid, and mass is transferred from the solid to the fluid. These two phenomena are interrelated. The factors affecting the heat and mass transfer in the fluid bed takes place by convection. At one point to another within the fluid bed, one portion of the fluid with the product granulated in the fluid bed removes the added water or moisture that can be removed by temperature and humidity.

S THE NOZZLE

&lt; d PARTICLE

d DROPLET &gt; d PARTICLE

DRIED ON  
PARTICLES

(ACCELERATION)

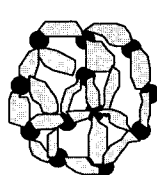
F binding &lt; F break-up

GROWTH BY LAYERING

&gt; F break-up

ABLE GROWTH  
MERATION

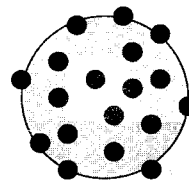
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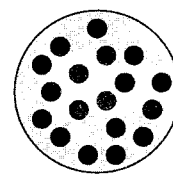
Pendular



Funicular



Capillary



Droplet

Fig. 10 States of liquid saturation.

depends on the droplet size of the binder solution. As the liquid addition continues, more and more nuclei agglomerate and continue the transition from the pendular state to the capillary state.

The uniqueness of the fluid bed agglomeration process is how the liquid addition and drying (evaporation) steps are concurrently carried out. When the granulation liquid is sprayed onto a fluidized bed, the primary particles are wetted and form, together with the binder, relatively loose and very porous agglomerates. Densification of these agglomerates is brought about solely by the capillary forces present in the liquid bridges. Therefore, it is important that the quantity of liquid sprayed onto the bed should be relatively large compared with that used in high shear granulation.

Drying a wet product in a fluid bed is a separate topic, but during the granulation process it becomes an integral part of the process; hence, understanding fluid bed drying is important before we review the agglomeration process.

## V. FLUID BED DRYING

Drying is usually understood to be removal of moisture or solvent; it involves heat and mass transfer. Heat is transferred to the product to evaporate liquid, and mass is transferred as a vapor in the surrounding gas; hence, these two phenomena are interdependent. The drying rate is determined by the factors affecting the heat and mass transfer. The transfer of heat in the fluid bed takes place by convection. Convection is the transfer of heat from one point to another within a fluid (gas, solid, or liquid) by the mixing of one portion of the fluid with another. The removal of moisture from a product granulated in the fluid bed granulator or in other equipment essentially removes the added water or solvent. This *free moisture content* is the amount of moisture that can be removed from the material by drying at a specified temperature and humidity. The amount of moisture that remains associated

with the material under the drying conditions specified is called the *equilibrium moisture content* (EMC).

The evaporation rate of liquid film surrounding the granule being dried is related to the rate of heat transfer by the following equation:

$$\frac{dw}{dt} = h \cdot \frac{A}{H} \cdot \Delta T$$

where  $dw/dt$  is the mass transfer rate (drying rate),  $h$  is the heat transfer coefficient,  $A$  is the surface area,  $H$  is the latent heat of evaporation, and  $\Delta T$  is the temperature difference between the air and the material surface.

Because fluid bed processing involves drying of a product in suspended hot air, the heat transfer is extremely rapid. In a properly fluidized processor, product temperature and the exhaust air temperatures should reach equilibrium. Improper air distribution, hence, poor heat transfer in fluidized bed, causes numerous problems such as caking, channeling, or sticking. The capacity of the airstream (gas) to absorb and carry away moisture determines the drying rate and establishes the duration of the drying cycle. Control of this capacity is the key to controlling the drying process. The two elements essential to this control are inlet air temperature and airflow. The higher the temperature of the drying air, the greater its vapor-holding capacity. Because the temperature of the wet granules in a hot gas depends on the rate of evaporation, the key to analyzing the drying process is psychrometry [34–36].

*Psychrometry* is defined as the study of the relations between the material and energy balances of water vapor–air mixtures. Psychrometric charts (Fig. 11) simplify the crucial calculations of how much heat must be added and how much moisture can be added to the air. The process of drying involves both heat and mass transfer. For drying to occur, a concentration gradient must exist between the moist granule and the surrounding environment. As in heat transfer, the maximum rate of mass transfer that occurs during drying is proportional to the surface area, turbulence of the drying air, the driving force between the solid and the air, and the drying rate. Because heat energy must be supplied to evaporate the moisture, the driving force for mass transfer is the same one required for heat transfer, which is the temperature difference between the air and the solid.

Schaefer and Worts [37] have shown that the higher the temperature difference between incoming air and the product, the faster the drying rate. Therefore, product temperature should be monitored closely to control the fluidized bed-drying process.

During fluid bed drying, the product passes through three distinct temperature phases (Fig. 12). At the beginning of the drying process, the material heats up from the ambient temperature to approximately the wet bulb temperature of the air in the dryer. This temperature is maintained until the

## Batch Fluid Bed Granulation

ASHRAE PSYCHROMETRIC CHART NO. 3  
HIGH TEMPERATURE 10°C to 120°C SEA LEVEL  
BAROMETRIC PRESSURE 101.325 kPa  
COPYRIGHT 1982  
AMERICAN SOCIETY OF HEATING, REFRIGERATING AND AIR-CONDITIONING ENGINEERS

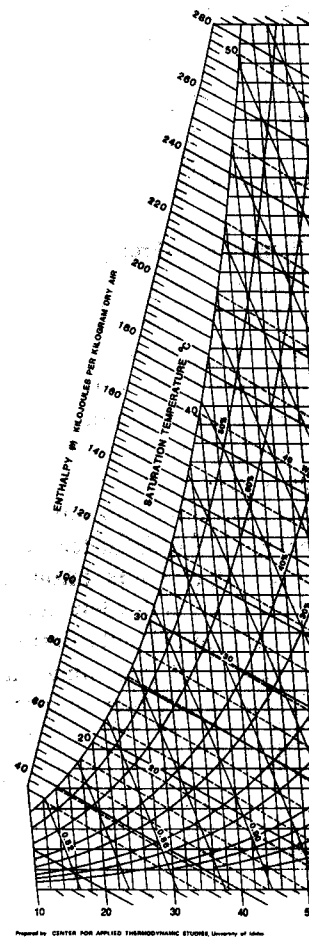


Fig. 11 Psychrometric chart

ns specified is called the *equilib-*

rounding the granule being dried  
following equation:

ing rate),  $h$  is the heat transfer  
tent heat of evaporation, and  $\Delta T$   
ir and the material surface.  
drying of a product in suspended  
In a properly fluidized processor,  
emperatures should reach equilib-  
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ASHRAE PSYCHROMETRIC CHART NO. 3  
HIGH TEMPERATURE 10°C to 120°C SEA LEVEL  
BAROMETRIC PRESSURE 101.325 kPa



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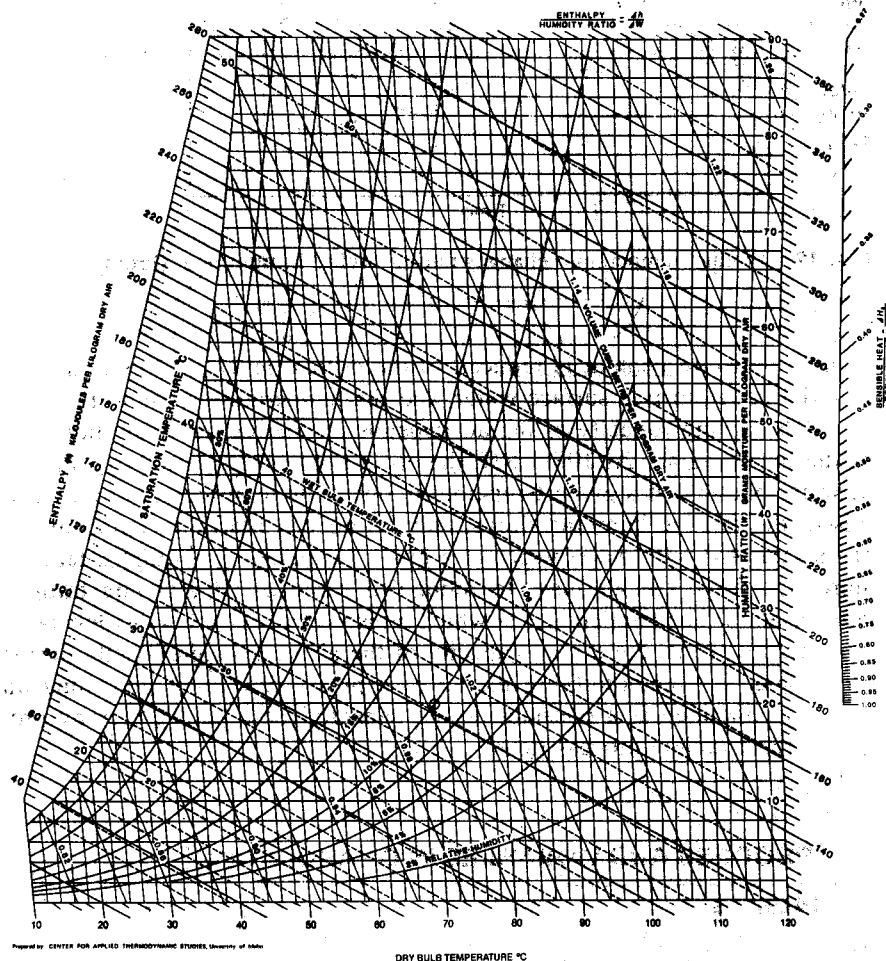
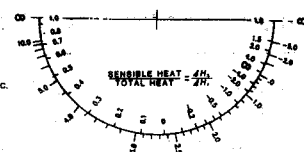


Fig. 11 Psychrometric chart.

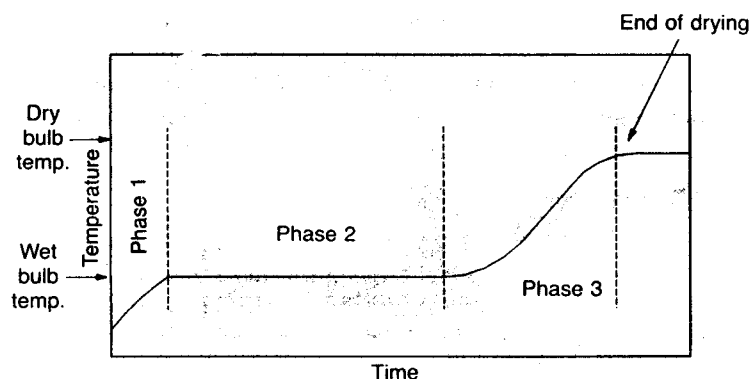


Fig. 12 Product temperature changes during drying in fluid bed. (From Ref. 20.)

granule moisture content is reduced to the critical level. At this point, the material holds no free surface water, and the temperature starts to rise.

The drying capacity of the air depends on the relative humidity (RH) of the incoming air. At 100% RH, the air is holding the maximum amount of water possible at a given temperature, but if the temperature of the air is raised, the relative humidity drops, and the air can hold more moisture. If air is saturated with water vapor at a given temperature, a drop in temperature will force the air mass to relinquish some of its moisture through condensation. The temperature at which moisture condenses is the dew point temperature. Thus, the drying capacity of the air varies significantly during processing. By dehumidifying the air to a preset dew point, incoming air can be maintained at a constant drying capacity (dew point), thereby providing reproducible process times.

## VI. PROCESS AND VARIABLES IN GRANULATION

### A. Process

As with any granulating system in fluid bed granulation processing, the goal is to form agglomerated particles through the use of binder bridges between the particles. To achieve a good granulation, particles must be uniformly mixed, and liquid bridges between the particles must be strong and easy to dry. Therefore, this system is sensitive to the particle movement of the product in the unit, the addition of the liquid binder, and the drying capacity of the air. The granulation process in the fluid bed requires a binary nozzle, a solution delivery system, and compressed air to atomize the liquid binder.

## Batch Fluid Bed Granulation

Figure 13 shows the equipment used for batch fluid bed granulation.

Thurn [38], in a 1970 study, investigated the effects of glomerating, and drying on the granulation process. Results indicated that the granulation process is a function of the airflow rate and air volume, and the raw materials, such as

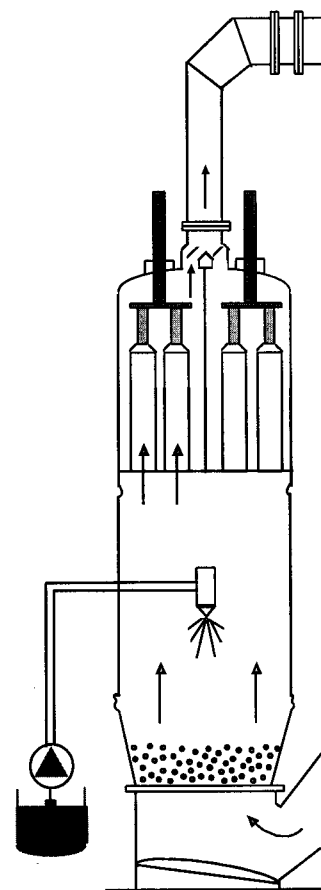
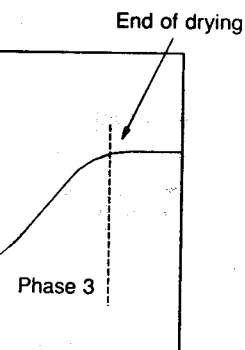


Fig. 13 A typical fluid bed



drying in fluid bed. (From Ref. 20.)

critical level. At this point, the temperature starts to rise. As the temperature rises, the relative humidity (RH) of the air is holding the maximum amount of moisture. If the temperature of the air is increased, the air can hold more moisture. If the temperature is decreased, a drop in temperature causes some of its moisture through condensation. The dew point of the air varies significantly during the drying process. If the incoming air is at a preset dew point, the drying capacity (dew point), thereby pro-

## GRANULATION

In granulation processing, the goal is to use binder bridges between particles. For this to happen, particles must be uniformly sized and strong enough to withstand particle movement of the product. The drying capacity of the fluid bed requires a binary nozzle, a liquid binder, and air to atomize the liquid binder.

Figure 13 shows the equipment setup for granulation using the fluid bed processor.

Thurn [38], in a 1970 thesis, investigated details of the mixing, agglomerating, and drying operations that take place in the fluid bed process. Results indicated that the mixing stage was particularly influenced by the airflow rate and air volume. It was suggested that the physical properties of the raw materials, such as hydrophobicity, may exert a strong influence on

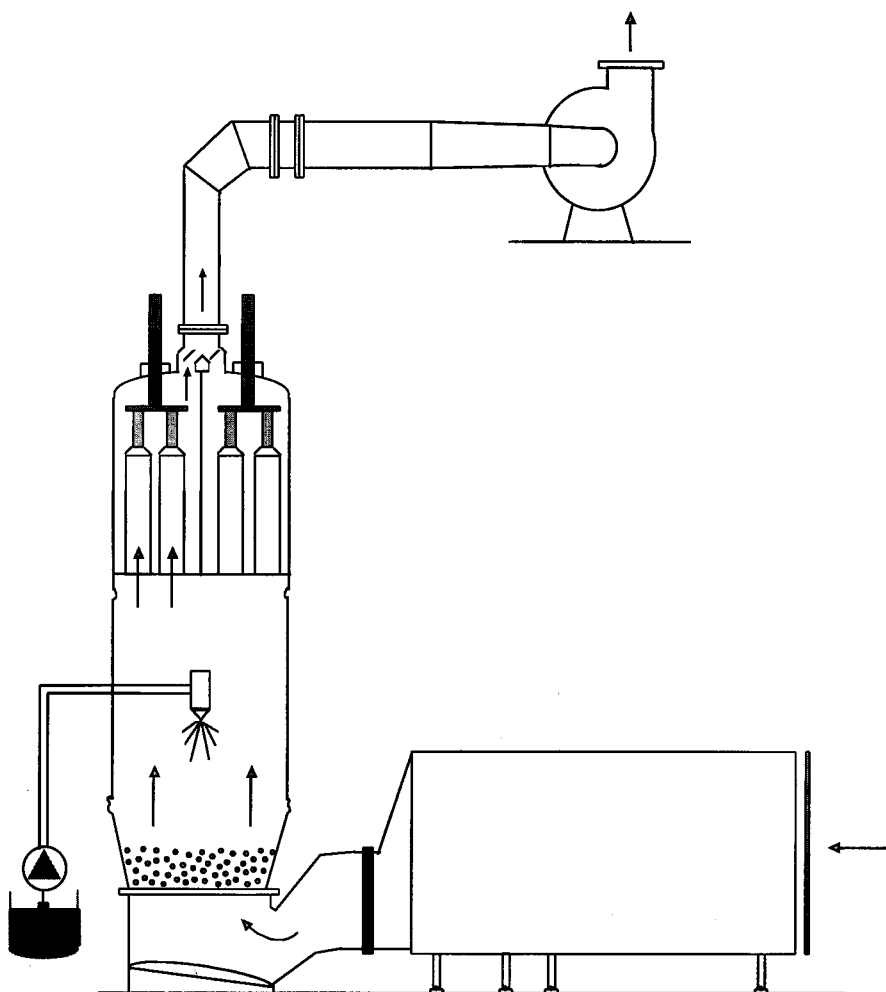


Fig. 13 A typical fluid bed processor setup for fluid bed granulation process.



particular attention was paid to design (two-fluid) nozzle gave homogeneous granule. The need for granule formation, and it was materials required particular attention published on the influence of raw [3,50,55-65], binder concentra- [59,62-64,66-82].

must be carefully controlled to liquid is sprayed into a fluid and form, together with the operates. Densification of these by the capillary forces present that a relatively large quantity in high or low shear granule bed. During spraying, a portion tion; thus, the system has little phase. The particle size of the bed by adjusting the quantity of (i.e., the droplet size).

les depends principally on the granulated and the type of the lower fluidizing air temperature, er spray rate produced a better

process can be divided into three

ally, the particle properties de- particle density, a small particle shape that approaches spherical, stickiness during the process- large, particle size distribution, ity are some of the properties

that impact on the properties of the granules formed. The cohesiveness and static charges on particles present fluidization difficulty. The same difficulties were observed when the formulation contained hydrophobic material or a mixture of hydrophilic and hydrophobic materials. The influence of hydrophobicity of primary particles has been shown by Aulton and Banks [17], who demonstrated that the mean particle size of the product was directly related to wettability of the primary particles expressed as  $\cos \Theta$  (where  $\Theta$  is the contact angle of the particles). It was also reported that as the hydrophobicity of the mix is increased, a decrease in granule growth is observed. Aulton and associates, in a later publication, showed that addition of a surface-active agent, such as sodium laurel sulfate, improves the fluidized bed granulation [54]. In a mixture containing hydrophobic and hydrophilic primary particles, granule growth of hydrophilic materials takes place selectively, creating content uniformity problems. Formulating a controlled-release granulation can be accomplished by using fluid bed granulation. A controlled-release matrix formulation of naproxin was successfully developed by using fluid bed granulation [86].

*b. Low-Dose Drug Content.* Wan et al. [87] studied various methods of incorporating a low-dose drug, such as chlorphenamine maleate, in a lactose formulation with polyvinyl pyrrolidone (povidone; PVP) as the granulating solution. They concluded that the randomized movement of particles in the fluid bed may cause segregation of the drug and that uniform drug distribution was best achieved by dissolving the drug in granulating solution. The mixing efficiency of drug particles with the bulk material increased, in proportion to the granulating liquid used to dissolve the drug. The optimum nozzle-atomizing pressure was deemed to be important to avoid spray-drying the drug particles or overwetting, which creates uneven drug distribution. Higashide et al. [88] studied fluidized bed granulation using 5-fluorouracil in concentration of 0.3% in 1:1 mixture of starch and lactose; hydroxypropylcellulose (HPC) was used as the binder. The ratios of starch and lactose contained in the granules were measured gravimetrically. The researchers found a larger amount of the drug and starch in larger granules than in smaller granules. The results were attributed to the hydrophobicity of the 5-fluorouracil and starch, and the hydrophilicity of lactose.

*c. Binder.* A more general discussion on the types of binders used in the pharmaceutical granulations and their influence on the final granule properties is presented in Chapter 4 of this book. Different binders have different binding properties and the concentration of individual binder may have to be changed to obtain similar binding of primary particles. Thus, the type of binder, the binder content in the formulation, and the concentration of the



binder have major influence on granule properties. These properties include friability, flow, bulk, density, porosity, and size distribution.

Davies and Gloor [89,90] reported that the types of binder, such as PVP, acacia, gelatin, and HPC, all have different-binding properties that affect the aforementioned final granule properties. Hontz [80] investigated the effects of microcrystalline cellulose concentration, inlet air temperature, binder (PVP) concentration, and binder solution concentration on tablet properties; and found that the binder and microcrystalline cellulose concentration had a significant effect on the tablets' properties. Alkan and Ulusoy [65] studied binder (PVP) addition in solution and as a dry powder in the powder mix. They found a larger mean granule size when the dry binder was granulated with ethanol. However, when the binder was in solution the granules produced were less friable and more free-flowing. This same finding was confirmed by other researchers [81,82]. Binder temperature affects the viscosity of the solution and, in turn, affects the droplet size. Increased temperature of the binder solution reduces the viscosity of the solution, thereby reducing the droplet size and producing a smaller mean granule size. Binder solution viscosity and concentration affect the droplet size of the binder. Polymers, starches, and high molecular weight PVP cause increased viscosity which, in turn, creates larger droplet size and, subsequently, larger mean granule particle size [57].

Diluted binders are preferred because they facilitate finer atomization of the binder solution, provide the control of the particle size, reduce the friability, and increase the bulk density even though the tackiness or binding strength may suffer [8,58,68,72,90].

*d. Binder Solvent.* In most instances water is used as a solvent. The selection of solvent, such as aqueous or organic, depends on the solubility of the binder and the compatibility of product being granulated. Generally, organic solvents, because of their rapid vaporization from the process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization, as shown in Table 1. The requirement of solvent for the binder can be eliminated by incorporating binder, or a mixture of binders, of low melting point and incorporating it with the drug substance in the dry form. The temperature of the incoming air is sufficient to melt the binder and form the granules.

## 2. Equipment Related Variables

*a. Design.* The availability of the fluid bed processors from different suppliers of the equipment is essentially similar. The differences in design of different suppliers sometime provides difficulty in scaling-up from the laboratory units to a production units in a linear scale.

**Table 1** Heat of Vaporization

Solvent	Bo
Methylene chloride	
Acetone	
Methanol	
Ethanol	
Isopropanol	
Water	

To fluidize and thus of process air is required. on the amount of material capacity of the process air tained constant throughout of equipment provide high cannot maintain the same portionality, reduces the dr resulting in longer process of the fluid bed is modula granulating, coating, rotop changing the container tha

*b. Air Distributor Pl*  
caused by random fluidiza granulation process. Optim dized particles. This is a co dizing conditions and a p during the process. As the plenum of the batch fluid air determines how fluidiza

Perforated air-distrib stainless steel screen, desc supplying air to the produ of open area. Air distributo available. These interchang such that batches of variou form quality. To prevent optimum lift properties. F quires low fluidizing veloc

properties. These properties include size distribution.

that the types of binder, such as different-binding properties that properties. Hontz [80] investigated concentration, inlet air temperature, solution concentration on tablet microcrystalline cellulose concentrations' properties. Alkan and Ulusoy ion and as a dry powder in the granule size when the dry binder in the binder was in solution the are free-flowing. This same finding [82]. Binder temperature affects effects the droplet size. Increased s the viscosity of the solution, ing a smaller mean granule size. n affect the droplet size of the ular weight PVP cause increased et size and, subsequently, larger

they facilitate finer atomization of the particle size, reduce the though the tackiness or binding

water is used as a solvent. The ganic, depends on the solubility act being granulated. Generally, orization from the process, pro- lution. Different solvents have n Table 1. The requirement of incorporating binder, or a mixture rating it with the drug substance coming air is sufficient to melt

d bed processors from different nilar. The differences in design fficulty in scaling-up from the near scale.

**Table 1** Heat of Vaporization for Commonly Used Solvents

Solvent	Boiling point (°C)	Density (g/mL)	Heat of vaporization (kcal/g)
Methylene chloride	40.0	1.327	77.0
Acetone	56.2	0.790	123.5
Methanol	65.0	0.791	262.8
Ethanol	78.5	0.789	204.3
Isopropanol	82.4	0.786	175.0
Water	100.0	1.000	540.0

To fluidize and thus granulate and dry the product, a certain quantity of process air is required. The volume of the air required will vary, based on the amount of material that needs to be processed. The ratio of drying capacity of the process air to the quantity of the product needs to be maintained constant throughout the scaling-up process. However, some suppliers of equipment provide higher drying capacity for their laboratory unit, but cannot maintain the same ratio for the production units. This lack of proportionality, reduces the drying capacity per unit volume of the process air, resulting in longer process time in the production units. The current design of the fluid bed is modular, for which multiple processes, such as drying, granulating, coating, rotoprocessing, and such, can be carried out by simply changing the container that is specially designed for the process.

*b. Air Distributor Plate.* The process of agglomeration and attrition caused by random fluidization requires control of the particle during the granulation process. Optimization of the process requires control over fluidized particles. This is a complex phenomenon owing to the prevailing fluidizing conditions and a particle size distribution, that undergoes changes during the process. As the conditioned air is introduced through the lower plenum of the batch fluid bed, the fluidizing velocity of a given volume of air determines how fluidization will be achieved.

Perforated air-distributor plates covered with the 60- to 325-mesh fine stainless steel screen, described previously, provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air distributors plates that have 4–30% open area are normally available. These interchangeable plates provide a range of loading capacities such that batches of various sizes can be produced efficiently and with uniform quality. To prevent channeling, an operator can select a plate with optimum lift properties. For example, a product with low-bulk density requires low fluidizing velocity. A distributor plate having a small open area

to give large enough pressure drop may provide uniform fluidization of such a product without reaching entraining velocity and impinging the process filters. Alternatively, a product with higher-bulk density can be fluidized and processed using a plate with a larger open area. The air distributor plate consists of a perforated plate and a fine-mesh screen. This arrangement sometimes causes problems, such as product leakage owing to a torn screen, and difficulty in cleaning without separating the perforated plate and the fine-mesh screen. To overcome these deficiencies, an overlap gill plate has recently been introduced. These plate designs were discussed earlier in the chapter.

*c. Pressure Drop.* The airflow through the fluid bed processor is created by the blower or a fan located downstream from the process chamber. This fan imparts motion and pressure to air by a paddle-wheel action. The moving air acquires a force or pressure component in its direction of motion because of its weight and inertia. This force is called *velocity pressure* and is measured in inches or millimeters of  $H_2O$ . In operating duct systems, a second pressure, which is independent of air velocity or movement, is always present. Known as *static pressure*, it acts equally in all directions. In exhaust systems, such as fluid bed processors, a negative static pressure exists on the inlet side of the fan. Total pressure is thus a combination of static and velocity pressures. Blower size is determined by calculating the pressure drop ( $\Delta P$ ) created by all the components of the fluid bed-processing system. Proper selection of a blower is essential in fluid bed design. A blower with an appropriate  $\Delta P$  will fluidize the process material adequately. However, a blower without enough  $\Delta P$  will not allow proper fluidization of the product, resulting in longer process time and improper granulation. A similar effect can be seen when a product with unusually high-bulk density is processed in place of normal pharmaceutical materials, or when an air distributor plate offering high resistance owing to its construction. This creates a pressure drop that the blower was not designed to handle. A properly sized blower or fan should develop a  $\Delta P$  sufficient for the exhaust damper to be used in the 30–60% open position. Any additional components, such as scrubbers, exhaust HEPA, police filters, or additional components in the air-handling unit, would require a larger blower and static pressure, which can be recommended by the supplier of the fluid bed processor.

*d. Shaker and Blow-Back Cycle Mechanism.* To retain entrained particles of a process material, process filters are used. To keep these filters from building up layers of fine process material, causing a higher pressure drop and, thus, improper fluidization, these filters are cleaned during the granulation process. When bag filters are used, mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation

of airflow and thus the fluidization with a single-bag house, this fluidization takes place. This time. To avoid process interruption is desired, so that the granulation process is also achieved by stainless steel filter bags in filters. Generally, filters should be changed at a certain step, to incorporate the fines. The cleaning frequency is high and Rawley [91] reported the effect of the possibility of improving the time and the corresponding

The following general granulation is recommended.

*Single-shaker unit:* The

5–10 s for shaking granules and the frequency can the duration of shaking should be kept at a

*Multiple shaker unit:*

frequency of shaking between filter cleaning pressure blow-back cleaning is about 10

*Cartridge filters:* The

cleaning frequency

The cleaning frequency of an automated system in which on time, the trigger point for cleaning across the filters. This automated

*e. Other Miscellaneous*

etry is considered to be a granulation process. The fluidization velocity in the bowl by more than half impinging onto the filter, creating fines in the bowl. Generally, a fluid bed chamber is preferred in which the air distributor plate to the top of the equipment offer units with a

provide uniform fluidization of such velocity and impinging the process bulk density can be fluidized and an area. The air distributor plate mesh screen. This arrangement prevent leakage owing to a torn screen, closing the perforated plate and the deficiencies, an overlap gill plate has designs were discussed earlier in the

gh the fluid bed processor is cre-stream from the process chamber. air by a paddle-wheel action. The component in its direction of motion ce is called *velocity pressure* and  $\frac{1}{2}\rho V^2$ . In operating duct systems, a velocity or movement, is always equally in all directions. In exhaust negative static pressure exists on thus a combination of static and ned by calculating the pressure the fluid bed-processing system. fluid bed design. A blower with material adequately. However, a proper fluidization of the product, per granulation. A similar effect y high-bulk density is processed s, or when an air distributor plate truction. This creates a pressure handle. A properly sized blower he exhaust damper to be used in components, such as scrubbers, components in the air-handling ic pressure, which can be recom-processor.

anism. To retain entrained par-are used. To keep these filters terial, causing a higher pressure e filters are cleaned during the sed, mechanical means are used he bag filters requires a cessation

of airflow and thus the fluidization during the filter-cleaning process. In units with a single-bag house, this results in a momentary *dead bed*, in which no fluidization takes place. This interruption in the process extends the process time. To avoid process interruptions, a multishaking filter bag arrangement is desired, so that the granulation process is continuous. The continuous process is also achieved by use of bag filters with a blow-back, or use of stainless steel filter bags in which air under pressure is pulsed through the filters. Generally, filters should be cleaned frequently during the granulation step, to incorporate the fines in the granulation. This is possible if the cleaning frequency is high and the period between the filter cleaning is short. Rawley [91] reported the effect of bag-shake-interval cycle. He discussed the possibility of improving particle size distribution by optimizing the shake time and the corresponding interval between bag shakes.

The following general guidelines for filter-cleaning frequency and duration is recommended.

*Single-shaker unit:* The frequency is 2–10 min between filter cleaning, 5–10 s for shaking. This may vary, because the fine powders form granules and the frequency between the shakes can be extended, as can the duration of shaking interval. In any event, the dead bed time should be kept at a minimum in a single-shaker unit.

*Multiple shaker unit:* Because this is a continuous process, the frequency of shaking for each section is approximately 15–30 s between filter cleanings, and about 5 s for shaking the filters. If a low-pressure blow-back system is used for the bags, the frequency of cleaning is about 10–30 s.

*Cartridge filters:* These offer continuous processing and require a cleaning frequency of 10–30 s.

The cleaning frequency and cleaning duration is now offered as an automated system in which instead of having to base the cleaning frequency on time, the trigger point for filter cleaning is the buildup of a pressure drop across the filters. This automates the process and eliminates operator input.

*e. Other Miscellaneous Equipment Factors.* Granulator bowl geometry is considered to be a factor that may impact on the agglomeration process. The fluidization velocity must drop from bottom to the top rim of the bowl by more than half to prevent smaller, lighter particles from impinging onto the filter, creating segregation from heavier product components in the bowl. Generally, a conical shape of the container and expansion chamber is preferred in which the ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multiprocessor concept, for which a single unit

can be used for drying, agglomerating, air suspension coating, or rotoprocessing, by changing the processing container, whereas the rest of the unit is common. This approach does eliminate the concerns about the geometry of the processor; because of the way these units are constructed.

### 3. Process-Related Variables

*Agglomeration* is a dynamic process during which a droplet is created by a two-fluid nozzle and is deposited on a randomly fluidized particle. The binder solvent evaporates, leaving behind the binder. Before all of the solvent is evaporated, other randomized particles form bonds on the wet site. This process is repeated numerous times to produce the desired agglomerated product. There are several process variables that control the agglomeration. Those most important to consider are listed as follows:

1. Process inlet air temperature
2. Nozzle atomization air pressure and volume
3. Fluidization air velocity and volume
4. Liquid spray rate
5. Nozzle: position and number of spray heads
6. Product and exhaust air temperature
7. Filter porosity and cleaning frequency
8. Bowl capacity

These process parameters are interdependent and can produce a desirable product if this interdependency is understood. Inlet process air temperature is determined by the choice of binder vehicle—whether aqueous or organic—and the heat sensitivity of the product being agglomerated. Generally, aqueous vehicles will permit the use of temperatures between 60 and 100°C. On the other hand, organic vehicles will require the use of temperatures from 50°C to lower than room temperature. Higher temperature will produce rapid evaporation of the binder solution and will produce smaller, friable granules. On the other hand, lower temperature will produce larger, fluffy, and denser granules. Figure 14 shows the relation of inlet and product air temperature and outlet air humidity during the granulation process.

The process of drying while applying spraying solution is a critical unit operation. This mass transfer step was previously discussed. The temperature, humidity, and volume of the process air determines the drying capacity. If the drying capacity of the air is fixed from one batch to the next, then the spray rate can also be fixed. If the drying capacity of the air is too high, the binder solution will have a tendency to spray dry before it can effectively form bridges between the primary particles. If, on the other hand, the drying capacity of the air is too low, the bed moisture level will become

### Batch Fluid Bed Granulation

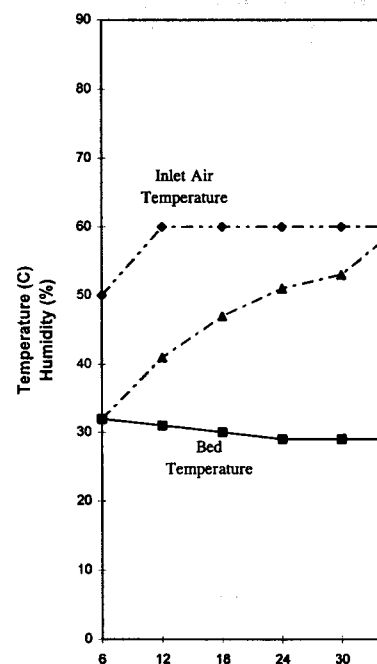


Fig. 14 Temperature and humidity during granulation.

too high, and particle growth will be in unacceptable movement or

The appropriate process parameters such as spray rate are critical to achieving uniform distribution and granule characteristics. Once proper operating parameters are determined, one can set the operating parameters for the processors.

1. Determine the proper spray rate and particle movement based on the airflow such that the product is dried.
2. Choose an inlet air temperature that accounts for weather effects (outdoor temperature). The air temperature

suspension coating, or rotopro-  
ner, whereas the rest of the unit  
the concerns about the geometry  
units are constructed.

which a droplet is created by a  
randomly fluidized particle. The  
the binder. Before all of the sol-  
les form bonds on the wet site.  
produce the desired agglomer-  
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spraying solution is a critical  
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particles. If, on the other hand,  
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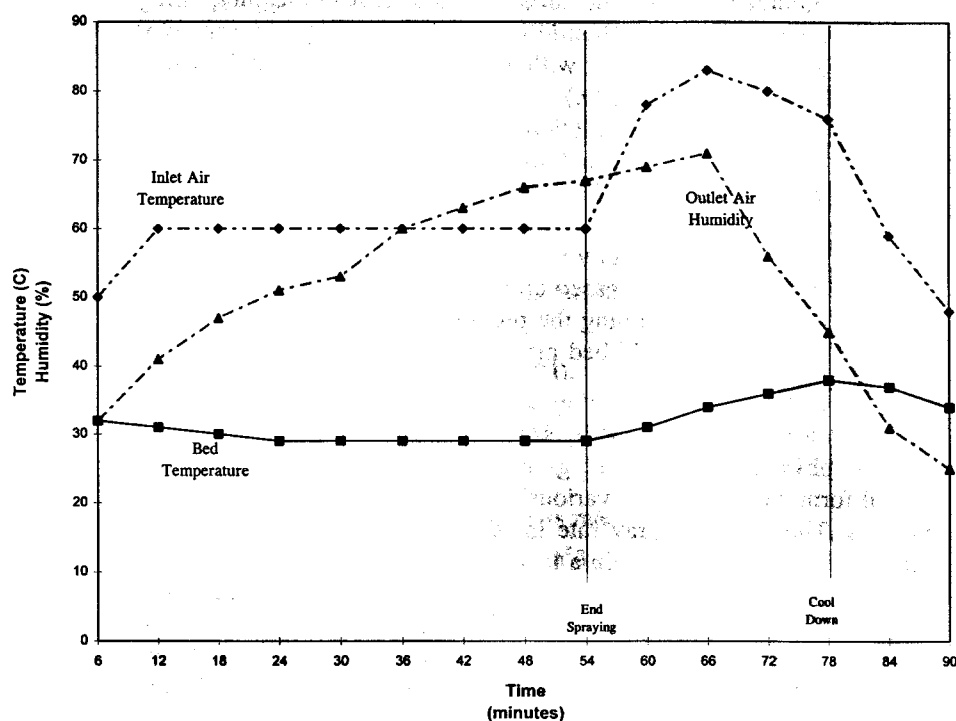


Fig. 14 Temperature and humidity changes during the granulation process.

too high, and particle growth may become uncontrollable. This will result in unacceptable movement of the product bed.

The appropriate process air volume, inlet air temperature, and binder spray rate are critical to achieving proper and consistent particle size distribution and granule characteristics. There are many ways to arrive at the proper operating parameters. The following procedure is one of the ways one can set the operating parameters when granulating with fluid bed processors.

1. Determine the proper volume of air to achieve adequate mixing and particle movement in the bowl. Avoid excessive volumetric airflow such that the particles are entrained into the filters.
2. Choose an inlet air temperature that is high enough to negate weather effects (outside air humidity or inside room conditions). The air temperature should not be detrimental to the product being

granulated. (To achieve a consistent yearround process, a dehumidification–humidification system is necessary, which provides the process air with a constant dew point and, hence, a constant drying capacity.)

3. Achieve a binder solution spray rate that will not dry while spraying (spray-drying) and will not overwet the bed. This rate should also allow the nozzle to atomize the binder solution to the required droplet size.
4. A typical air velocity used for spray granulation is from 1.0 to 2.0 m s<sup>-1</sup>. Table 2 is based on the psychrometric chart that gives a first guess at determining the proper spray rate for a spray granulation process in a fluid bed processor.

Variables in the fluid bed granulation process and its effect on the final granulation was summarized by Davis and Gloor [85], in which they state that the physical properties of granulation are dependent on both the individual formulations and the various operational variables associated with the process. The solution spray rate increases and subsequent increases in average granule size, resulted in a less friable granulation, higher bulk density, and a better flow property for a lactose–cornstarch granulation. Similar results were obtained by an enhanced binder solution, decreasing nozzle air pressure, or lowering the inlet air temperature during the granulation cycle. The position of the binary nozzle relative to the fluidized powders was also studied. It was concluded that, by lowering the nozzle, binder efficiency is enhanced, resulting in average granule size and a corresponding decrease in granule friability.

The significant process parameters and their effect on the granule properties are summarized in Table 3. Maroglou [33] listed various parameters affecting the type and rate of growth in batch fluidized granulation (Table 4) and showed the influence of process parameters and the material parameters on the product.

## VII. PROCESS CONTROLS AND AUTOMATION

The batch fluid bed agglomeration process requires accurate, repeatable control of all critical process parameters for a robust system. Earlier designs of the fluid bed processor used pneumatic control logic that provided safe operation in a hazardous area, but relied heavily on human actions to achieve repeatable product quality and accurate data acquisition. Current designs use programmable logic controllers (PLCs) and personal computers (PCs) to achieve sophisticated control and data acquisition. The operating conditions

## Batch Fluid Bed Granulation

**Table 2** Calculation of Fluid

Given process data

Air volume range:

Minimum (1.2 m/s)

Maximum (1.8 m/s)

Inlet air temperature and humidity

% solids in sprayed solution

From psychrometric chart

Air density at point where

Inlet air absolute humidity

Maximum outlet air absolute

(follow line of constant wet

Use 100% outlet RH for

column coating

Calculations for spray rate

Step 1. Convert air volumetric

Minimum \_\_\_\_\_ m<sup>3</sup>/h ÷

Maximum \_\_\_\_\_ m<sup>3</sup>/h ÷

Step 2. Subtract inlet air humidity

\_\_\_\_\_ (g H<sub>2</sub>O/kg air) H<sub>2</sub>O

Step 3. Calculate (minimum

(This will provide a range

airflow used in the unit.)

Step 1 (minimum) \_\_\_\_\_

Step 1 (maximum) \_\_\_\_\_

are controlled to satisfy product critical data is collected at end-of-batch report.

Access to all user-controlled passwords, permitting access at a security level, not only authentication of each valid record verified before any operation end-of-run report. The user

sistent yearround process, a system is necessary, which prevents dew point and, hence, a con-

te that will not dry while spray-erwet the bed. This rate should be binder solution to the required

y granulation is from 1.0 to 2.0 psychrometric chart that gives a first spray rate for a spray granulation

process and its effect on the final Gloor [85], in which they state are dependent on both the individual variables associated with the and subsequent increases in aggranulation, higher bulk density, instarch granulation. Similar resolution, decreasing nozzle air re during the granulation cycle. the fluidized powders was also the nozzle, binder efficiency is and a corresponding decrease in

their effect on the granule prop- [33] listed various parameters ch fluidized granulation (Table meters and the material param-

## OMINATION

quires accurate, repeatable con- robust system. Earlier designs of control logic that provided safe op- y on human actions to achieve acquisition. Current designs use personal computers (PCs) to ition. The operating conditions

**Table 2** Calculation of Fluid Bed Spray Rate

Given process data

Air volume range:

Minimum (1.2 m/s) \_\_\_\_\_ m<sup>3</sup>/h

Maximum (1.8 m/s) \_\_\_\_\_ m<sup>3</sup>/h

Inlet air temperature and humidity to be used: \_\_\_\_\_ °C \_\_\_\_\_ % RH

% solids in sprayed solution \_\_\_\_\_ % solids

From psychrometric chart

Air density at point where air volume is measured: \_\_\_\_\_ m<sup>3</sup>/kg air

Inlet air absolute humidity (H): \_\_\_\_\_ g H<sub>2</sub>O/kg air

Maximum outlet air absolute humidity (H): \_\_\_\_\_ g H<sub>2</sub>O/kg air

(follow line of constant adiabatic conditions)

Use 100% outlet RH for spray granulator or 30–90% (as required) for column coating

Calculations for spray rate

Step 1. Convert air volumetric rate to air mass rate

Minimum \_\_\_\_\_ m<sup>3</sup>/h ÷ (60 × \_\_\_\_\_ m<sup>3</sup>/kg air) = \_\_\_\_\_ kg air/min

Maximum \_\_\_\_\_ m<sup>3</sup>/h ÷ (60 × \_\_\_\_\_ m<sup>3</sup>/kg air) = \_\_\_\_\_ kg air/min

Step 2. Subtract inlet air humidity from outlet air humidity:

\_\_\_\_\_ (g H<sub>2</sub>O/kg air) H out – \_\_\_\_\_ (g H<sub>2</sub>O/kg air) H in =  
\_\_\_\_\_ g H<sub>2</sub>O removed/kg air

Step 3. Calculate (minimum and maximum) spray rate of solution:

(This will provide a range of generally acceptable spray rates based on the airflow used in the unit.)

Step 1 (minimum) \_\_\_\_\_ × step 2 \_\_\_\_\_ ÷ [1 – (\_\_\_\_\_ % solids ÷ 100)] =  
\_\_\_\_\_ spray rate (g/min) at minimum airflow

Step 1 (maximum) \_\_\_\_\_ × step 2 \_\_\_\_\_ ÷ [1 – (\_\_\_\_\_ % solids ÷ 100)] =  
\_\_\_\_\_ spray rate (g/min) at minimum airflow

are controlled to satisfy parameters of multiple user-configured recipes, and critical data is collected at selected time intervals for inclusion in an end-of-batch report.

Access to all user-configured data is protected by security levels with passwords, permitting access to only selected functions. With the appropriate security level, not only are operating conditions configured, but also identification of each valid recipe and operator is entered. The identification is verified before any operator actions are permitted and is included with the end-of-run report. The use of computer-related hardware requires some ad-



**Table 3** Effect of Process Parameters on Granular Properties

Process parameter	Effect on process	Refs.
Inlet air temperature	Higher inlet temperature produces finer granules, and lower temperature produces larger, stronger granules.	72,83
Humidity	Increase in air humidity causes larger granule size, longer drying times.	37
Fluidizing airflow	Proper airflow should fluidize the bed without clogging the filters. Higher air flow will cause attrition and rapid evaporation, generating smaller granules and fines.	17,20,72
Nozzle and nozzle height	A binary nozzle produces finest droplets and is preferred. The size of the orifice has an insignificant effect except when binder suspensions are to be sprayed. Optimum nozzle height should cover the bed surface. Too close to the bed will wet the bed faster, producing larger granules, whereas too high a position will spray-dry the binder, create finer granules, and increase granulation time.	57
Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size and, hence, the granule size. Higher liquid flow rate will produce larger droplet and larger granules and the reverse will produce smaller granules. At a given pressure, an increase in orifice size will increase droplet size and liquid throughput.	37,57,85, 92
Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity, and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.	17,54,71, 72,92

ditional validation, but with coordination between the control system provider and the end user, the validation of software can be managed. Figure 15 shows the pneumatic control panel and Fig. 16 a PLC-based control panel with a typical operator screen.

The most important sensors for control of the drying process are inlet and exhaust air temperature and the sensor for airflow measurement, located

**Table 4** Parameters Affecting Granulation

**A. Operating parameters**  
Droplet size

Bed moisture content

Attrition

Solution (binder)  
concentration

**B. Material parameters**  
Solution (binder)  
concentration  
Type of binder  
Wettability

Material to be granulated

\*NAR is the ratio of air to liquid, expressed either in mass units or in volume units.

<sup>b</sup>Especially important relative to the material to be granulated.

in the air transport system. The parameters are product temperature; the number of drops (across the inlet filter) processed, and outlet process filter-cleaning frequency.

## Molecular Properties

Process	Refs.
... produces finer granules. ... temperature produces ...	72,83
... causes larger granule ...	37
... fluidize the bed without ... Higher air flow will ... rapid evaporation, gen- ...	17,20,72
... produces finest droplets and ... of the orifice has an ... except when binder sus- ...	57
... Optimum noz- ... over the bed surface. ... will wet the bed fas- ... granules, whereas too ... spray-dry the binder, ... and increase granula- ...	
... the compressed air. ... must be kept con- ... droplet size and, hence, ... her liquid flow rate ... droplet and larger gran- ... will produce smaller ... pressure, an increase ... crease droplet size and ...	37,57,85, 92
... by liquid flow rate, ... atomizing air pressure ... r the droplet, the ... average granules.	17,54,71, 72,92

between the control system pro-  
software can be managed. Figure  
g. 16 a PLC-based control panel

l of the drying process are inlet  
or airflow measurement, located

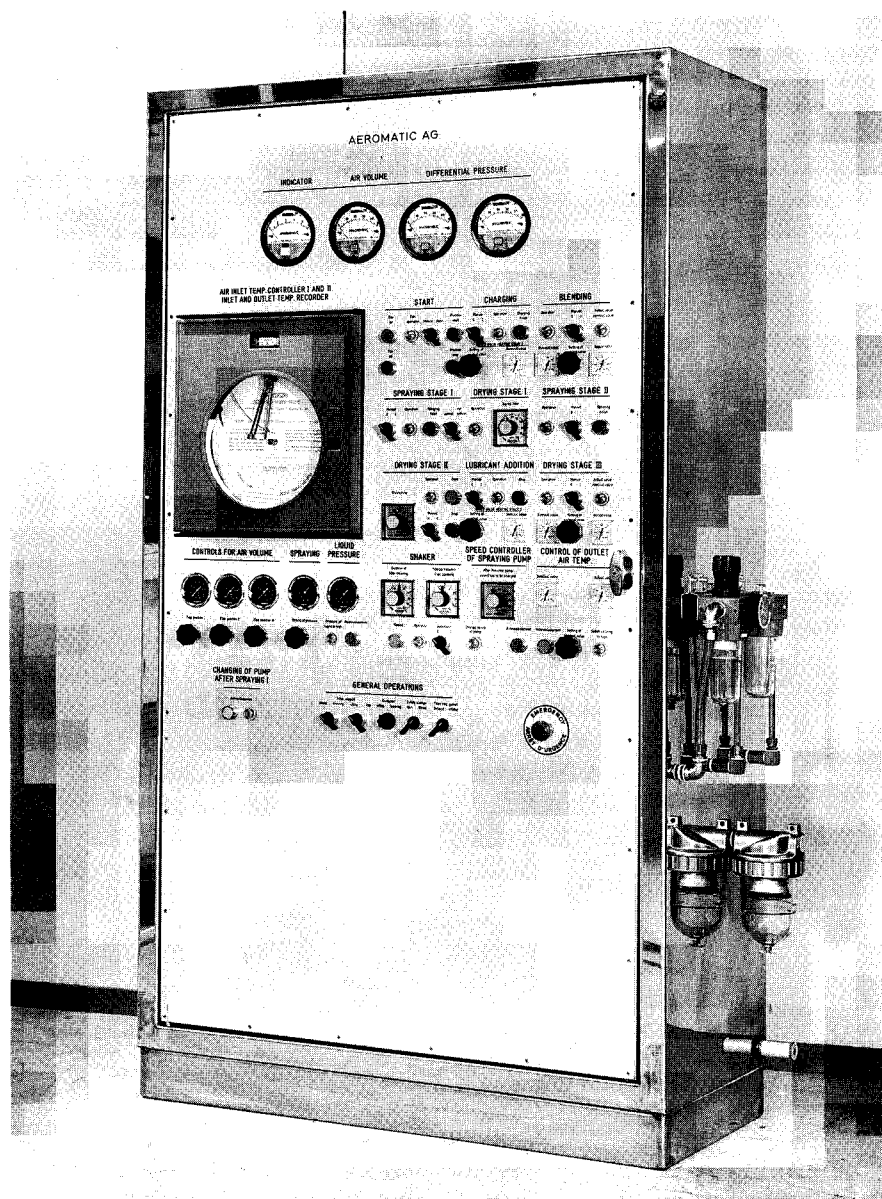
**Table 4** Parameters Affecting the Type and Rate of Growth in Batch Fluidized Granulation

A. Operating parameters	
Droplet size	NAR <sup>a</sup> Atomization air velocity Rheology Surface tension Nozzle position Nozzle type
Bed moisture content	Solution type and feed rate Bed temperature Fluidization velocity
Attrition	Fluidization velocity Aspect ratio Nozzle position and atomization air velocity Distributor design Jet grinding
Solution (binder) concentration	Bridge strength and size Rheology
B. Material parameters	
Solution (binder) concentration	Bridge strength and size Rheology
Type of binder	Molecular length and weight
Wettability	Particle-solvent interaction Surface tension Viscosity
Material to be granulated	Average size Size distribution <sup>b</sup> Shape Porosity Drying characteristics Density and density difference <sup>b</sup>

<sup>a</sup>NAR is the ratio of air to liquid flow rates through the nozzle of a twin fluid atomizer expressed either in mass units or in volume units (air at STP).

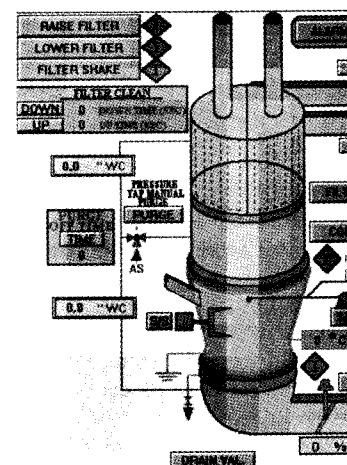
<sup>b</sup>Especially important relative to elutriation and segregation.

in the air transport system. Other sensors for the spray agglomeration process are product temperature; the atomization air pressure and volume; pressure drops (across the inlet filter, the product container with the product being processed, and outlet process air filter); inlet air humidity or dew point; process filter-cleaning frequency and duration; spray rate for the binder so-



**Fig. 15** Pneumatic control panel. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

## Batch Fluid Bed Granulation



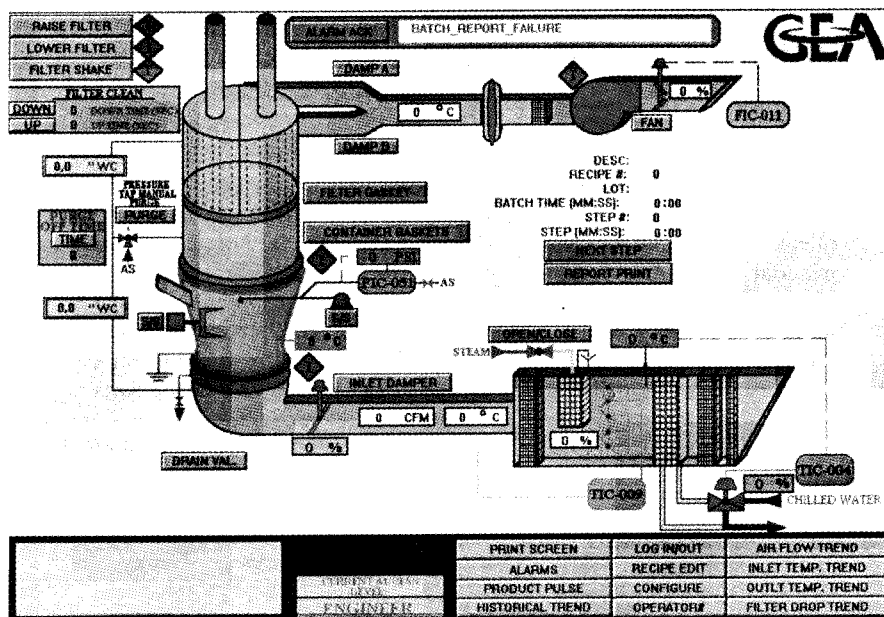
**Fig. 16** PLC-based screen process of Niro Inc., Aeromatic-Fielder Division.

lution; and total process time information to the computer. The computer's memory and to recall data analysis, a gre

## VIII. PROCESS SCALE-

### A. Regulatory

Scale-up is normally identified until a desired level of production. The Association of Pharmaceutical Drug Administration (FDA) has several speakers presented from a perspective. For example, Sherrill presented several categories: those related to processing equipment and to ascertain whether or not char



lution; and total process time. All of these sensors provide constant feedback information to the computer. These electronic signals may then be stored in the computer's memory and then recalled as a batch report. With this ability to recall data analysis, a greater insight can be gained into the process.

### A. Regulatory

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. In 1991, the American Association of Pharmaceutical Scientists (AAPS) with the US Food and Drug Administration (FDA) held a workshop on scale-up [93], during which several speakers presented scale-up issues from an industrial and regulatory perspective. For example, Shangraw divided scale-up problems into two general categories: those related to raw materials or formulation, and those related to processing equipment. He also indicated that it is essential to ascertain whether or not changes in raw materials have occurred before one

looks at processing or equipment changes as a source of any problem. The workshop report as it pertains to the process and equipment is reproduced in the following:

It is generally recognized that many NDAs [New Drug Applications] and ANDAs [Abbreviated NDAs] contain provision for multiple manufacturers of the drug substance(s), and that not all drug substance suppliers, a priori, produce equivalent material. There is then a need for material quality control to assure the performance and reproducibility of the finished product. Particle size and distribution, morphology, and intrinsic dissolution of the drug substance are important considerations. Polymorphism, hygroscopicity, surface area, wettability, density (bulk and tapped), compressibility (for dry blending), and powder flow effects should be controlled.

Additionally, the process should be controlled by employment of a validation protocol, which defines the critical parameters and also establishes the acceptance criteria for the granulation or blend; which may include sieve analysis, flow, density, uniformity, and compressibility, moisture content, etc.

In the milling, blending, *granulating and or drying processes*, the operating principles of the equipment employed should be defined, and the variables determined. The impact and mechanism of measurement on in-process variables should be defined. Time, temperature, work input of equipment, blend/granulation volume, and granulating rate should be determined. . . . The parameters selected should be appropriate for the process, . . . . In those cases where the manufacturing process has been controlled and validated as specified in the foregoing discussion; batch scale-up, changes in site of manufacture, allowance for equipment change (where the operating principle is the same), minor formulation changes, etc., should be determined on the basis of the comparability of both the blend/granulation and the final product; as assured by: a) appropriate tests; b) specifications; c) process validation; and d) comparative accelerated stability.

Regulatory guidelines for scale-up and postapproval changes (SUPAC) IR, were released in 1995 [94] and are discussed in Chapter 16 of this book.

## B. Scale-up and Equipment Design

The scale-up from the laboratory equipment to production-sized units is dependent on equipment design, which may or may not have been scalable as far as its dimensional feature or components selection is concerned. The importance of scalability is well understood and accepted by the manufacturers of fluid bed processors. Various sizes in their product line are logically designated and manufactured. Airflow in the fluid bed process is a critical

parameter. The design and the laboratory and production of the drying capacity of a kilogram or liter of the product is linear. The other design features of the container and how it has been used by the manufacturer supplies. The containers can be used to control the cross-sectional area is designed to be linear.

## C. Scale-up and Process

The fluid bed agglomeration, dry mixing, spray agglomeration. These process steps are equivalent. The process is really determined by the constant building of granules which constant building of granules is taking place. Granule size is determined by granulation [37]; hence, control.

Gore et al. [83] studied the effect of scale-up during scale-up. They found that granule characteristics were determined by the rate of binder from the bed, rate of binder from the binder liquid.

The atomizing air pressure is the most important elements of the process. The pressure yields a finer droplet size as described earlier in this chapter. A major factor that affects the fluid bed granulation process is the pressure. To assure successful scale-up, the pressure of spray nozzle setup is critical. The study concluded that the most important nozzle's atomizing air pressure, atomizing air pressure, atomizing air pressure delivered to the nozzle tip. The volume measurement device is critical. The drying capacity of the product is determined by the size.

as a source of any problem. The process and equipment is reproduced

As [New Drug Applications] a provision for multiple manufacturing at not all drug substance supply. There is then a need for performance and reproducibility distribution, morphology, and are important considerations. Area, wettability, density (bulk density), and powder flow effects

controlled by employment of critical parameters and also granulation or blend; which uniformity, and compressibil-

and or drying processes, the employed should be defined, and mechanism of measurement Time, temperature, work input, and granulating rate should be appropriate for the manufacturing process has in the foregoing discussion; time, allowance for equipment (the same), minor formulation on the basis of the comparability of product; as assured by: a) process validation; and d) com-

postapproval changes (SUPAC) discussed in Chapter 16 of this book.

ent to production-sized units is or may not have been scalable when selection is concerned. The and accepted by the manufacturer in their product line are logically the fluid bed process is a critical

parameter. The design and selection of the processor is very important for the laboratory and production unit. Because airflow is one of the components of the drying capacity of a fluid bed system, the ratio of air volume per kilogram or liter of the product is very critical to achieve a scale-up that is linear. The other design feature is the cross-sectional area of the product container and how it has been designed throughout the various sizes that a manufacturer supplies. The relation between various sizes of the process containers can be used to calculate the scale-up of binder spray rate and, if the cross-sectional area is designed linearly, then the spray rate scale-up can be linear.

### C. Scale-up and Process Factors

The fluid bed agglomeration process is a combination of three steps: namely, dry mixing, spray agglomeration, and drying to a desired moisture level. These process steps are equally important; however, the quality of the granules is really determined during the spraying stage—the process during which constant building of granules and evaporation of binder solvent are taking place. Granule size is directly proportional to the bed humidity during granulation [37]; hence, control of this humidity during scale-up is essential.

Gore et al. [83] studied the factors affecting the fluid bed process during scale-up. They found that the processing factors that most affected granule characteristics were process air temperature, height of the spray nozzle from the bed, rate of binder addition, and the degree of atomization of the binder liquid.

The atomizing air pressure and the wetness of the bed are two of the most important elements of fluid bed granulation. A higher-atomizing air pressure yields a finer droplet of binder solution. Therefore, granule growth, as described earlier in this section, will be affected by the atomizing air pressure. A major factor that must be considered during the scale-up of fluid bed granulation process is maintaining the same droplet size of the binder to assure successful scale-up. A more recent study [92] confirmed the influence of spray nozzle setup parameters and the drying capacity of the air. The study concluded that more attention should be paid to the easily overlooked nozzle's atomizing air pressure and volume. When considering the atomizing air pressure, attention must be paid to ensure that enough air is delivered to the nozzle tip. This can be assured by placing air pressure and volume measurement devices at the nozzle. The data also show that the drying capacity of the process air influences the final granulated particles' size.

Jones [95] has suggested various process-related factors that should be considered during the scale-up of a fluid bed processing design. These suggestions follow:

Because of the higher degree of attrition in the larger unit, compared with the smaller one, the bulk density of the granulation from the larger fluid bed is approximately 20% higher than that of the smaller unit. He also emphasized the importance of keeping the bed moisture level below a critical moisture level to prevent the formation of larger agglomerates. Because, in a larger unit, the higher airflow, along with the temperature (drying capacity) provide higher evaporation rates, one must maintain the drying capacity in the larger unit such that the bed temperature is similar to that of the smaller unit. This can be accomplished by increased spray rate, increased air temperature, increased airflow, or a combination of these variables, to obtain suitable results. Because the ratio of bed depth to the air distributor increases with the size of the equipment, the fluidization air velocity is kept constant by increasing the air volume. In the past, the scale-up was carried out by selecting "best-guess" process parameters. The recent trend is to employ the factorial and modified factorial designs and search methods. These statistically designed experimental plans can generate mathematical relations between the independent variables, such as process factors, and the dependent variables, such as product properties. This approach still requires an effective laboratory-pilot-scale development program and an understanding of the variables that affect the product properties.

In summary, when scaling-up, the following processing conditions should be similar to the pilot-scale studies:

1. The fluidization velocity of the process air through the system
2. The ratio of granulation spray rate to drying capacity of fluidization air volume
3. The droplet size of the binder spray liquid

Each of these values must be calculated from the results of the operation of the pilot-sized unit. Pilot-sized equipment studies should also be conducted over a wide range to determine the allowable operating range for the process.

#### D. Case Study

The following case study illustrates how a product is scaled-up from 15 to 150 kg in equipment supplied by Aeromatic when one understands the critical process parameters used in scaling-up.

A spray granulation process was developed for a common pharmaceutical compound. The granulation process involved the spraying of a 5% (w/w) binder solution onto the fluidized powder. Table 5 shows the data from the

#### Batch Fluid Bed Granulation

**Table 5** Scale-up of Fluid Bed

##### Process parameters

Airflow ( $\text{m}^3 \text{h}^{-1}$ )
Inlet air temperature ( $^{\circ}\text{C}$ )
Spray rate ( $\text{g min}^{-1}$ )
Nozzle air pressure (bar)
Container cross-sectional area ( $\text{m}^2$ )
Numbers of nozzles

15-kg run and resulting sucrose granulation process [84].

#### 1. Airflow Calculations

To maintain the same fluidization velocity, the spray rate must be increased, based on the ratio of the cross-sectional area. In this case, the cross-sectional area of the larger unit was  $0.77 \text{ m}^2$  and the smaller was  $0.06 \text{ m}^2$ . The spray rate was calculated as  $300 \times (0.77/0.06) = 3850 \text{ g min}^{-1}$  after considering the increase in the spray rate.

#### 2. Spray Rate Calculation

To maintain the same particle size, the spray rate must be increased 13 times the pilot unit's spray rate. This would result in a longer residence time. A similar droplet size is to maintain the same atomization pressure. Thus, the spray rate was increased 13 times, thereby obtaining a granulation process similar to the pilot-sized unit.

#### 3. Temperature Calculation

Finally, the required inlet temperature was reduced in ratio of air volume to spray rate. The inlet temperature was reduced to  $50^{\circ}\text{C}$  to avoid spray-drying. The spray rate used in this scale-up could be increased 13 times, which would result in the ability to scale-up the process to that of the pilot-sized unit.

**Table 5** Scale-up of Fluid Bed Granulation Process Parameters

Process parameters	15 kg	150 kg
Airflow ( $\text{m}^3 \text{h}^{-1}$ )	300	4000
Inlet air temperature ( $^{\circ}\text{C}$ )	55	50
Spray rate ( $\text{g min}^{-1}$ )	100	800
Nozzle air pressure (bar)	2.5	5
Container cross-sectional area of the base ( $\text{m}^2$ )	0.06	0.77
Numbers of nozzles	1	3

15-kg run and resulting successful 150-kg run conditions for a spray agglomeration process [84].

### 1. Airflow Calculations

To maintain the same fluidization velocity, the air volume in a larger unit must be increased, based on the cross-sectional area of the product bowl. In this case, the cross-sectional area of the base of the larger container was  $0.77 \text{ m}^2$  and the smaller was  $0.06 \text{ m}^2$ . The correct airflow should be calculated as  $300 \times (0.77/0.06) = 3850 \text{ CMH}$ . This number was further modified, after considering the increase in bed depth in a larger unit, to 4000 CMH.

### 2. Spray Rate Calculations

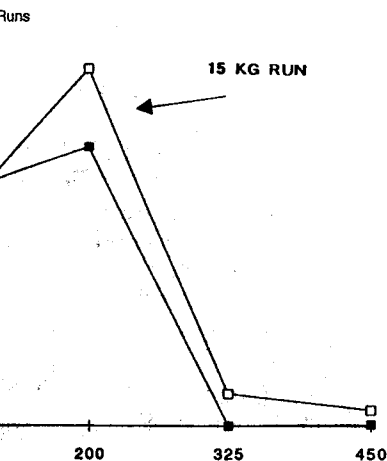
To maintain the same particle size, the triple-headed nozzle could spray three times the pilot unit's spray rate at a 2.5 atomization air pressure. However, this would result in a longer process time. Another approach to maintain the similar droplet size is to maintain the mass balance of spray rate and the atomization pressure. Thus, by increasing the atomization pressure to 5 bar, the spray rate was increased to  $800 \text{ g min}^{-1}$  keeping the same droplet size; thereby obtaining a granulation with the desired characteristics.

### 3. Temperature Calculations

Finally, the required inlet temperature was recalculated based on the change in ratio of air volume to spray rate. Because the air volume was increased over 13 times, but the spray rate was increased only 8 times, the inlet temperature was reduced to  $50^{\circ}\text{C}$ . This adjustment in drying capacity was necessary to avoid spray-drying of the spray solution. (The three-headed nozzle used in this scale-up could have been replaced by a six-headed nozzle. This would result in the ability to increase the spraying rate 13 times higher than that of the pilot-sized unit to match the airflow. The maintenance of droplet







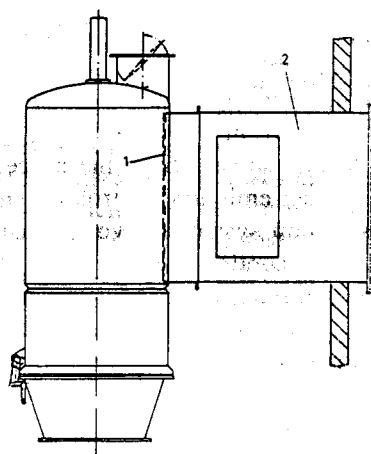
icle size distribution.

ved with the six-headed nozzle.  
ss time.) Figure 17 shows the  
15-kg unit and 150-kg unit.

n to occur: an ignition source, a  
n reacts with the fuel, releasing  
in free space, a fireball of con-  
n occurs in a closed container,  
mainly decided by the following  
xygen ratio, turbulence, precom-  
r, and ignition source. In a con-  
organic dust of sufficient fine-  
se to an overpressure of 10 bar.  
amount of air. This air, in the  
al for an explosion. This hazard  
nts. If sufficient ignition energy  
within the processor can take  
solvent-induced explosions, fluid  
withstand an overpressure of 2.0  
losion relief flaps, to release the

pressure as soon as it starts to build up inside the processor. The explosion flaps mounted either horizontally or vertically (Fig. 18a and b) are designed to vent the pressure buildup at as low as 0.06 bar. The explosion protection valve, shown in Figure 19a and b, acts to cut off the airflow to the blower and contain the overpressure within the processor. These explosion flaps open up to the outside of the building. These panels are gasketed, and sealed so normal fluid bed operation is not affected. It was accepted practice to have production units with a 2-bar-pressure shock integrity; however, the cleaning of the gasket area around the flaps is always difficult. With the introduction of potent and costly drug substances, the 2-bar design is being replaced with a 10-bar design. These units can withstand an explosion up to 10 bar. Most of the pharmaceutical dust explosion studied [96] show the overpressure reaching 9 bar with a  $K_{st}$  value (constant of explosion speed) of 200. An explosion in a 10-bar unit is contained within the unit. A 10-bar-designed unit does not require any explosion relief panels or gaskets. This eliminates the concerns about cleaning the gaskets and flaps. Another advantage of a 10-bar unit is, in case of explosion, the processor containing the potent drug substance is contained inside the unit, and an explosion does not pose an environmental problem, as with the 2.0-bar unit. A suppression system (see Fig. 19c) to combat the explosion hazard is alternatively used. This approach contains the explosion within the unit by suppressing the overpressure. The suppression system consists of low-pressure sensors located within the processor. These sensors are designed to trigger a series of fire extinguishers (containing ammonium phosphate), as soon as a preset level (generally 0.1 bar) of pressure is set within the processor.

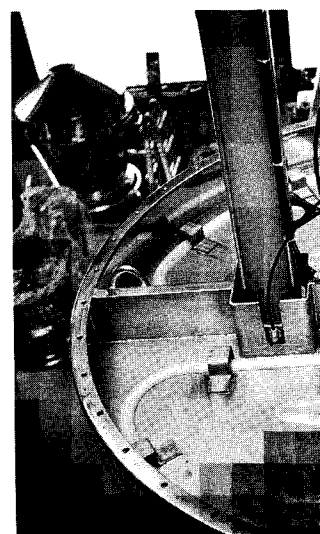
For a granulation requiring flammable solvents, process air and nozzle atomization air are replaced by an inert gas, such as nitrogen, and the system is designed as a closed cycle with the solvent recovery capability [97]. Various approaches can be taken to handle solvent from the process. Table 6 summarizes various methods for solvent emission control systems. Kulling and Simon [18] reported the closed-loop system shown in Figure 20. The inert gas used for fluidization circulates continuously. An adjustable volume of gas is diverted through the bypassed duct, where solvent vapors are condensed and solvent collected. The circulating gas passes through the heat exchanger to maintain the temperature necessary for evaporation of the solvent from the product bed. During the agglomeration and subsequent drying process, the solvent load in the gas stream does vary. The flow of the gas to the heat exchanger and the condenser is controlled by the bypass valve. By controlling the gas stream in this manner, the drying action is continued until the desired level of drying is reached. Even though the cost of fluid bed processor with the solvent recovery is generally double the cost of a



horizontal pressure relief

(a)

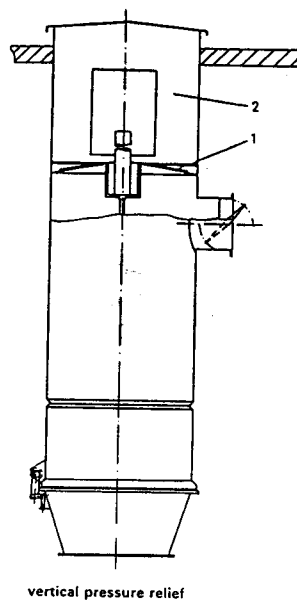
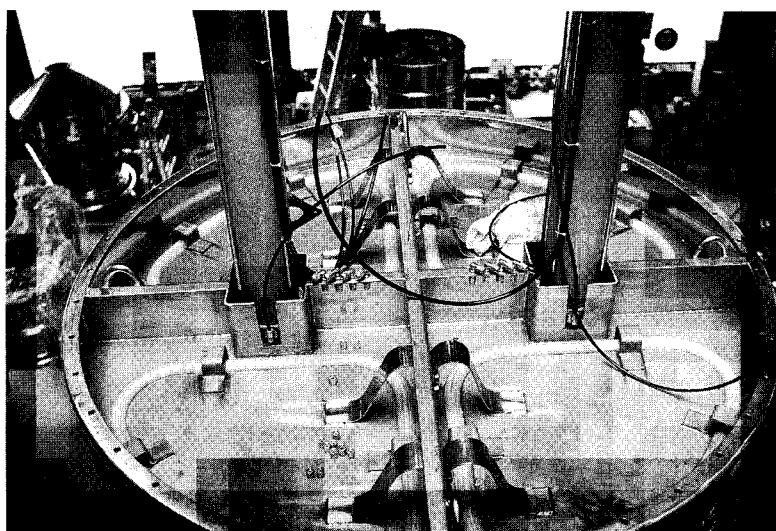
**Fig. 18** Processors with horizontal and vertical explosion relief panels. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)



vertical pressure relief

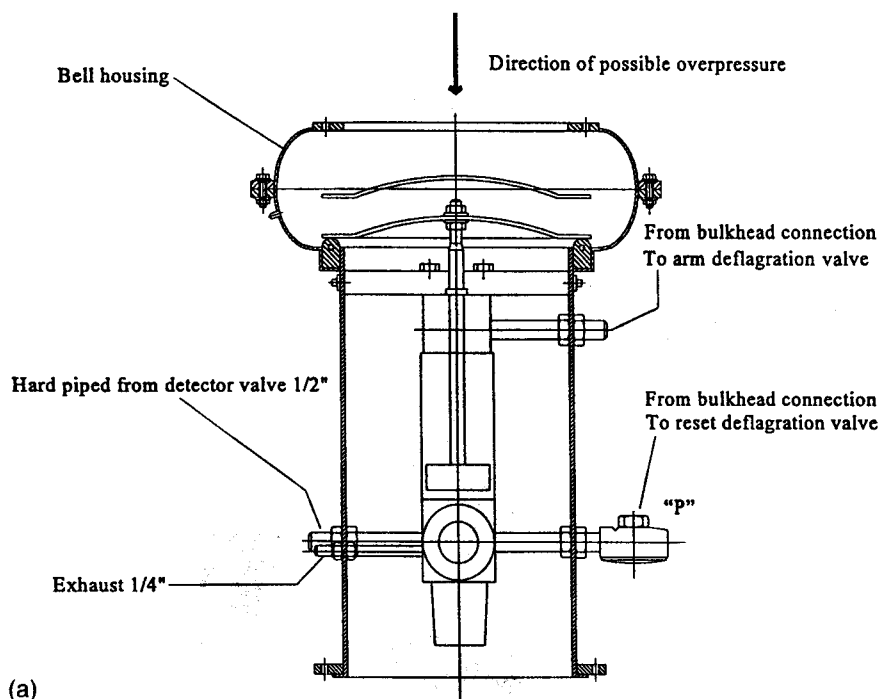
(b)

**Fig. 18** Continued



(b)

Fig. 18 Continued



**Fig. 19** (a) Schematic of an explosion protection valve; (b) explosion protection valve shown in the fluid bed installation; (c) explosion suppression system.

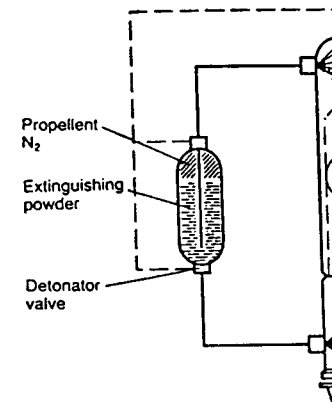
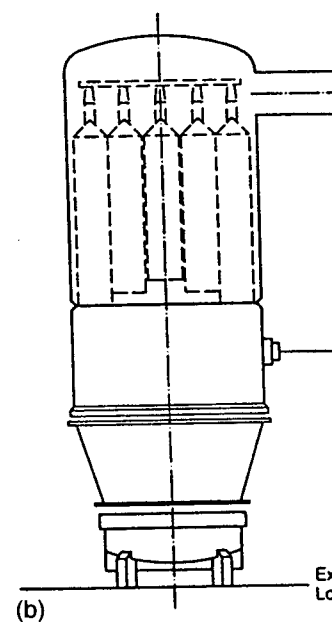
regular single-pass fluid bed processor, such a system offers effective measure for both explosion hazard reduction and an air pollution control.

## X. MATERIAL-HANDLING OPTIONS

The transfer of materials to and from the fluid bed processor is an important consideration. The loading and unloading of the processing bowl can be accomplished by manual mode or by automated methods.

### A. Loading

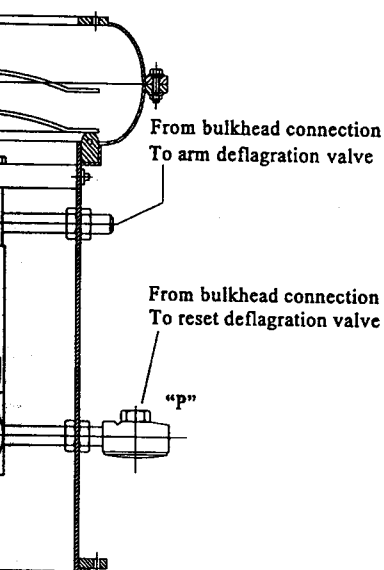
The traditional method for loading the unit is by removing the product bowl from the unit, charging the material into the bowl, and then placing the bowl back into the unit. This loading method is simple and cost-effective. Unfortunately, it has the potential of exposing the operators to the product and



(c)

**Fig. 19** Continued

Direction of possible overpressure



ction valve; (b) explosion protection  
xplosion suppression system.

ch a system offers effective mea-  
and an air pollution control.

uid bed processor is an important  
of the processing bowl  
nated methods.

is by removing the product bowl  
bowl, and then placing the bowl  
simple and cost-effective. Unfor-  
the operators to the product and

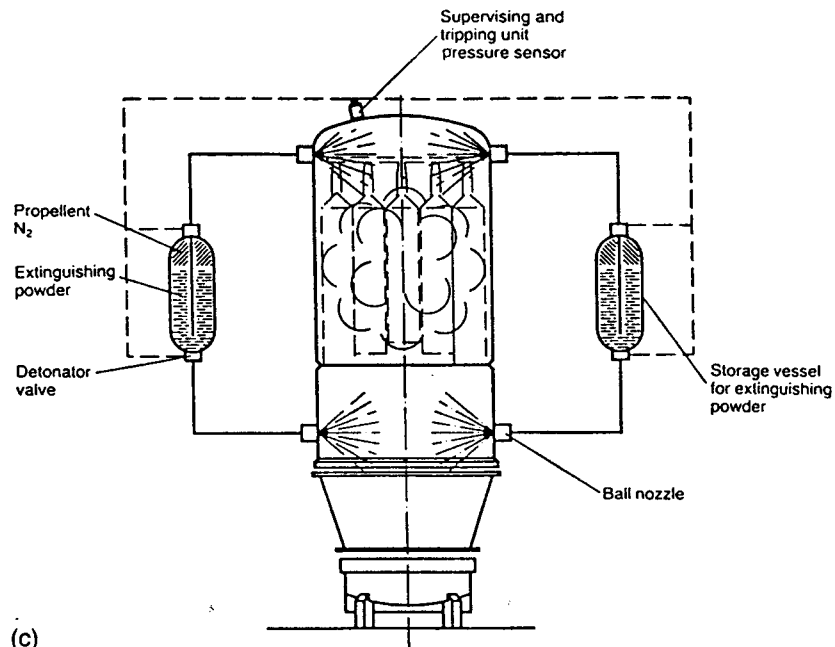
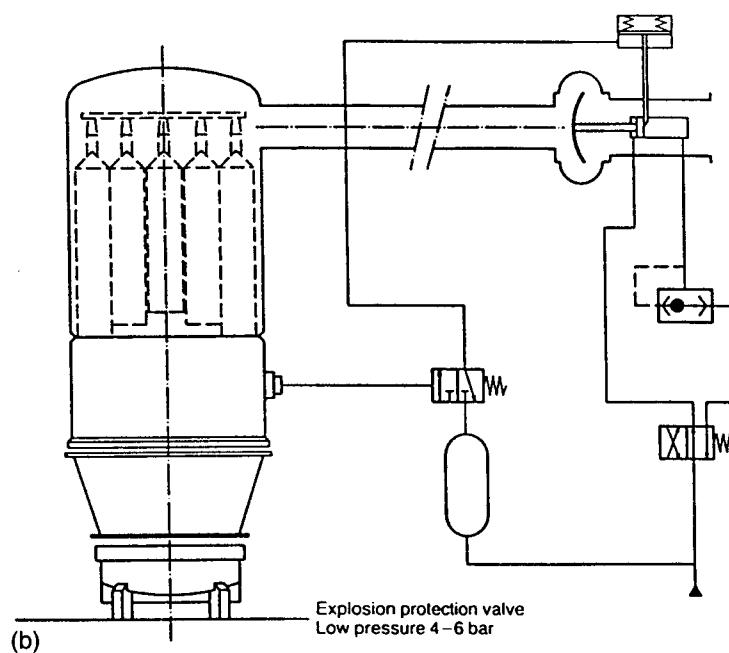


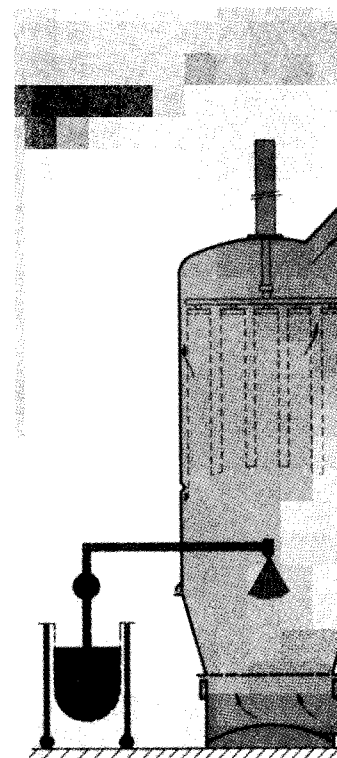
Fig. 19 Continued

**Table 6** Comparison of Different Solvent Emission Control System

Water scrubbing	Catalytic burning	Carbon absorption	Condensation
Open cycle High capital cost	Open cycle Low capital cost	Open cycle Moderate capital cost	Closed cycle/N <sub>2</sub> Low capital cost
High energy External installation	Low energy External installation	Low energy External installation	Low energy Internal installation
Medium space required	High space required	Moderate space required	Small space required
Medium flexibility	Medium flexibility	Low flexibility	Good flexibility
Waste treatment	CO <sub>2</sub> /H <sub>2</sub> O emissions waste treatment	Waste treatment	Concentrated waste

contaminating the working area. To avoid the product becoming a dust and cleaning hazard, a dust collection system should be installed to collect the dust before it spreads. A manual process also depends on the batch size, the operator's physical ability to handle the material, and the container full of product. Furthermore, this can be time-consuming because the material must be added to the product container, one material at a time.

The loading process can be automated and isolated to avoid worker exposure, minimize dust generation, and reduce loading time. There are two main types of loading systems. These systems are similar because both use the fluid bed's capability to create a vacuum inside the unit. Here the product enters the fluid bed through a product in-feed port on the side of the unit. This is done with the fan running and the inlet air control flap set so that minimum airflow may pass through the product container, and the outlet flap is almost fully open. Once the material has been charged to the fluid bed, the product in-feed valve is closed, and the granulating process started. This transfer method uses some amount of air to help the material move through the tube. Figure 21 shows the setup for loading the fluid bed. Loading can be done either vertically from an overhead bin, or from the ground. Less air is required through the transfer pipe when the material is transferred vertically, because gravity is working to help the process. Vertical transfer methods do require greater available height in the process area. Loading by this method has the advantages of limited operator exposure to the product, allows the product to be fluidized as it enters the processor; and reduces the loading time. The disadvantage of this type of system is the cleaning required between different products.



(a)

**Fig. 20** (a) Schematic of a c  
stallation of a solvent recovery  
Division.) Figure continues on

## B. Unloading

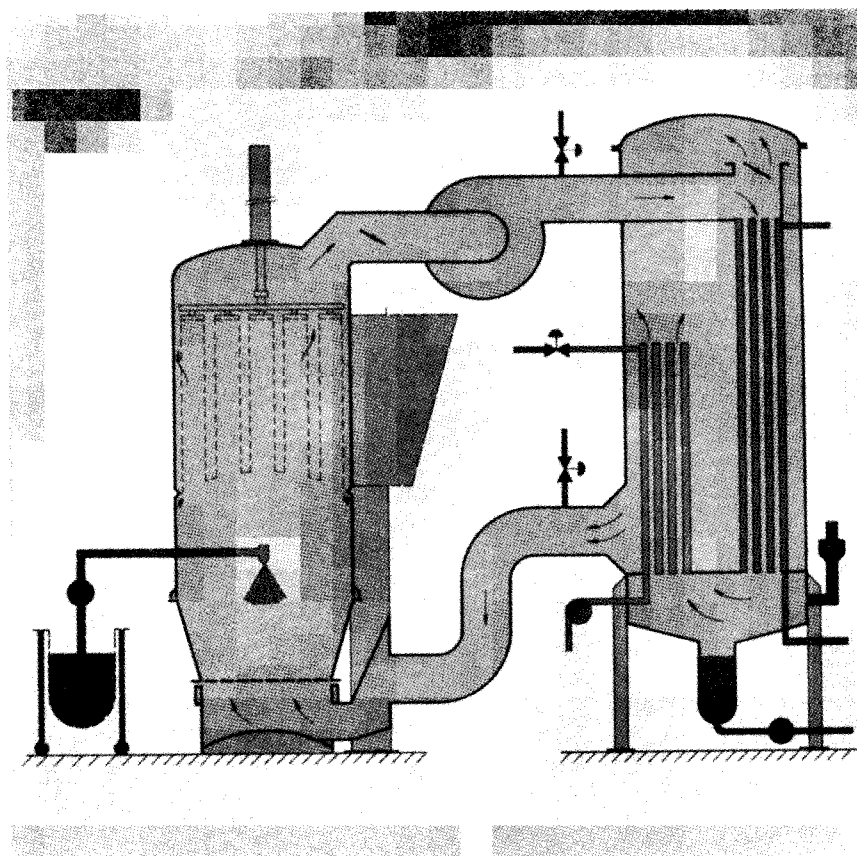
As with loading, the stand  
product bowl from the unit  
scoop the material from the  
impractical method because  
Alternatively, the product c  
tainer or unloaded by placin  
as shown in Figure 22. This

## Control System

Carbon absorption	Condensation
Open cycle	Closed cycle/ $N_2$
Moderate capital cost	Low capital cost
Low energy	Low energy
Internal installation	Internal installation
Moderate space required	Small space required
Good flexibility	Good flexibility
Waste treatment	Concentrated waste

the product becoming a dust and should be installed to collect the dust. This depends on the batch size, the material, and the container full of material because the material must be moved at a time.

and isolated to avoid worker exposure and reduce loading time. There are two systems similar because both use a closed-loop solvent recovery system inside the unit. Here the product is moved through a port on the side of the unit. The inlet air control flap is set so that the product container, and the outlet flap is set so that the product can be charged to the fluid bed, and the granulating process started. This helps the material move through the fluid bed. Loading can be done from the top, or from the ground. Less air is used in the process. Vertical transfer method is used in the process area. Loading by this method reduces the exposure to the product, and reduces the cleaning time of system is the cleaning re-



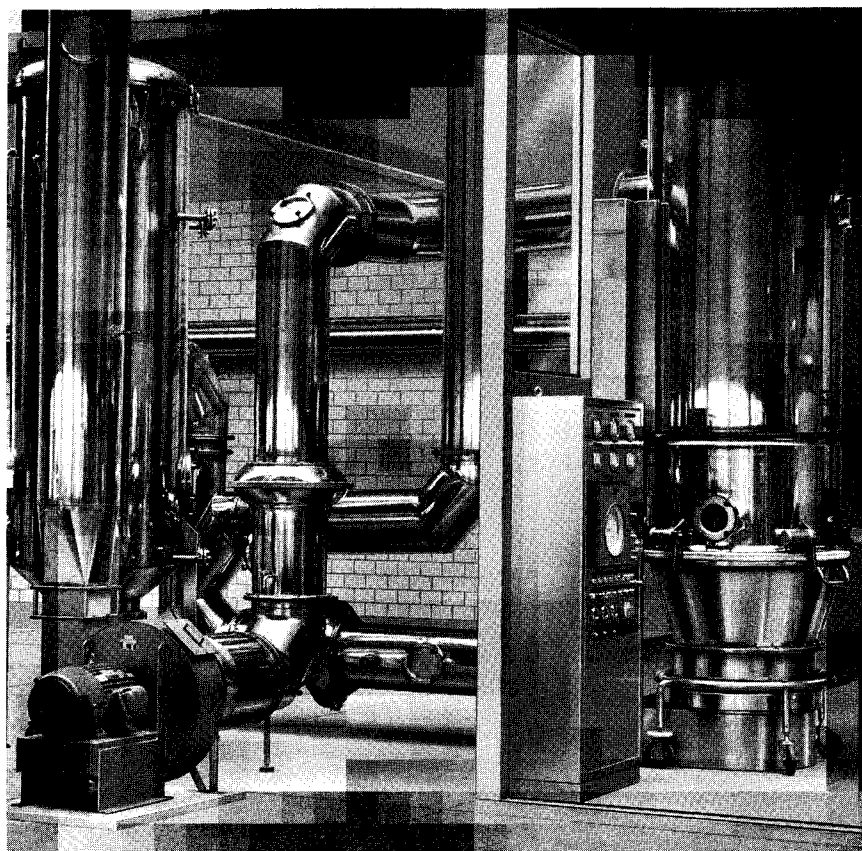
(a)

**Fig. 20** (a) Schematic of a closed-loop solvent recovery system; (b) typical installation of a solvent recovery system. (Courtesy of Niro Inc., Aeromatic-Fielder Division.) Figure continues on next page.

## B. Unloading

As with loading, the standard method for unloading is by removing the product bowl from the unit. Once the bowl is removed, the operator may scoop the material from the bowl, which is the most time-consuming and impractical method because of its potential for exposure to the product. Alternatively, the product can be vacuum transferred to a secondary container or unloaded by placing the product bowl into bowl-dumping device, as shown in Figure 22. This hydraulic device is installed in the processing

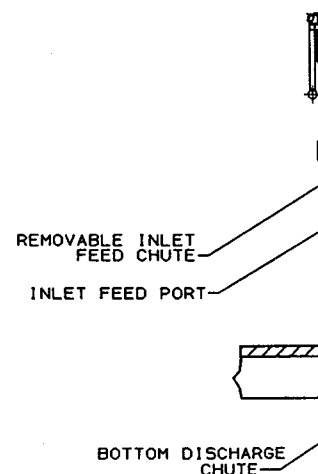




(b)

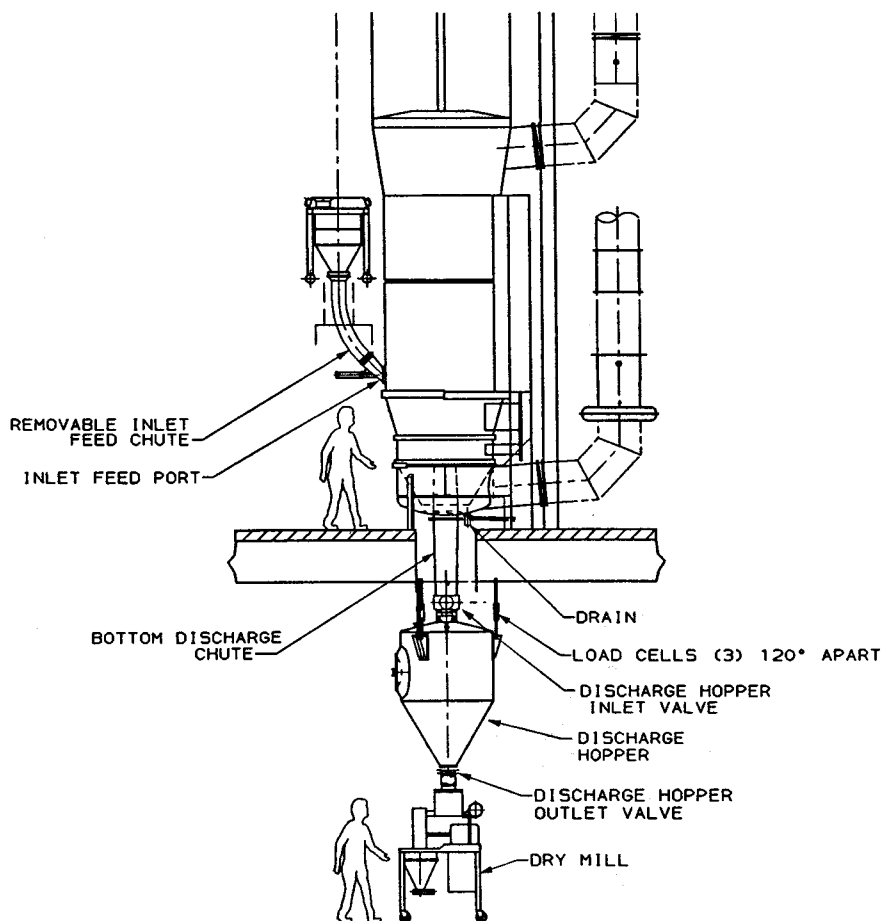
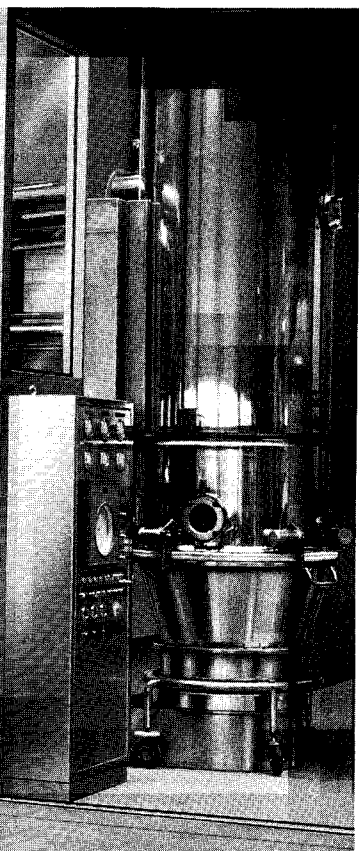
**Fig. 20** Continued

area. The mobile product container of the fluid bed processor is pushed under the cone of the bowl dumper and coupled together by engaging the toggle locks. Subsequently, the container is lifted hydraulically, pivoted around the lifting column, and rotated  $180^\circ$  for discharging. The use of the bowl-dumping device or vacuum-unloading device still requires that the product bowl be removed from the unit. There are contained and automated methods for unloading the product while the product bowl is still in the fluid bed processor. The product may either be unloaded out of the bottom of the product container or from the side. Until recently, the most common contained method was to unload the material from the bottom of the unit. This requires

**Fig. 21** Loading the fluid through the bottom of the fluid bed processor (Fielder Division.)

a ceiling that is high enough for the fluid bed granulation becomes a multistoried building.

There are two types of fluid bed granulation (Fig. 23). Gravity discharge granulation, which is located below the fluid bed processor, has a limitation preventing having a large transfer combination can be

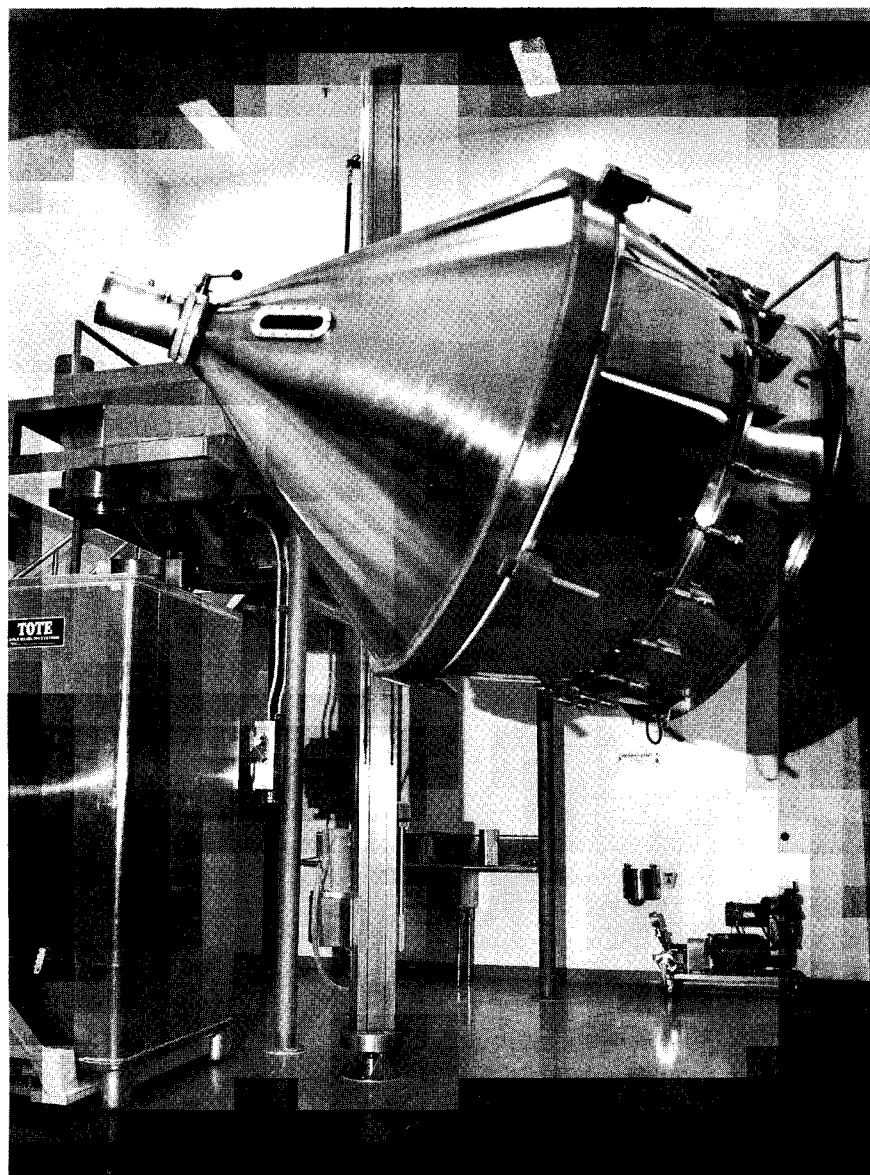


**Fig. 21** Loading the fluid bed through the product in-feed port and unloading through the bottom of the fluid bed processor. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

fluid bed processor is pushed under together by engaging the toggle hydraulically, pivoted around the base. The use of the bowl-dump design requires that the product bowl is still in the fluid bed processor out of the bottom of the product bowl, the most common contained bottom of the unit. This requires

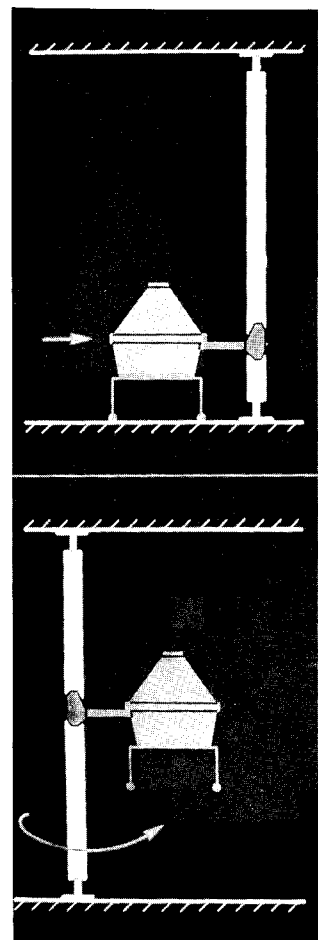
a ceiling that is high enough to accommodate the equipment, or the installation becomes a multistoried installation.

There are two types of bottom-discharge options: gravity or pneumatic (Fig. 23). Gravity discharge permits collection of the product into a container, which is located below the lower plenum. If the overall ceiling height limitation prevents having the discharge by gravity, the gravity-pneumatic transfer combination can be considered. The gravity discharge poses clean-



(a)

**Fig. 22** (a) Product discharge with bowl dumping device; (b) Mechanism of bowl lifting, raising, inverting, and bringing it down for discharging. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

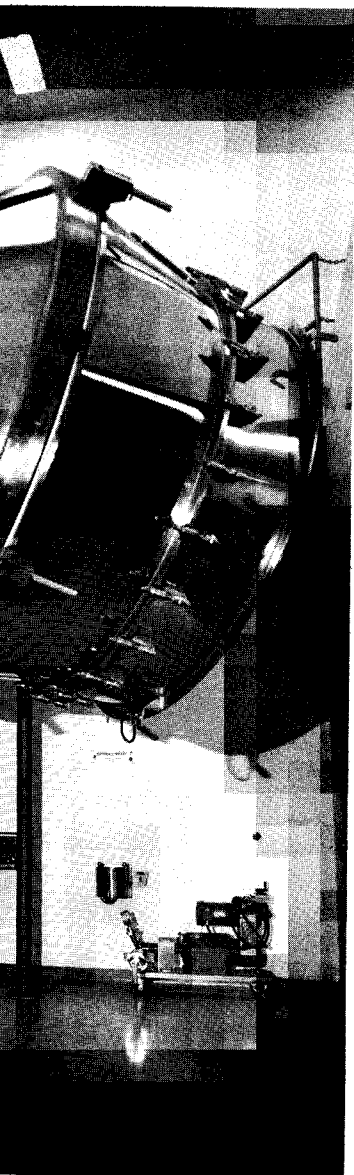


(b)

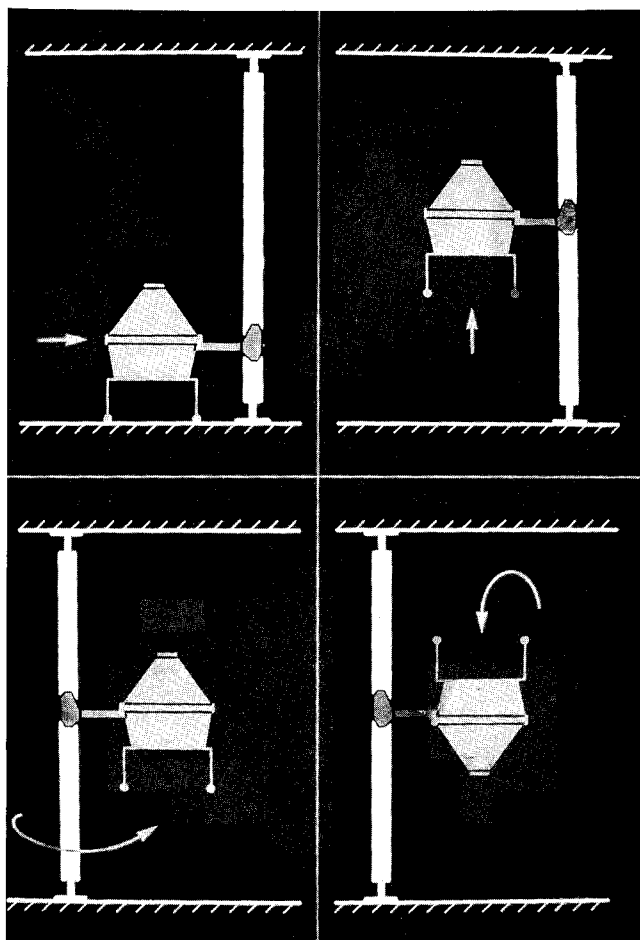
**Fig. 22** Continued

ing problems; because the same path, assurance of clear

The desire to limit the gill air distributor, mentioned in consideration of the side discharge gate (Fig. 24)



ing device; (b) Mechanism of bowl  
or discharging. (Courtesy of Niro

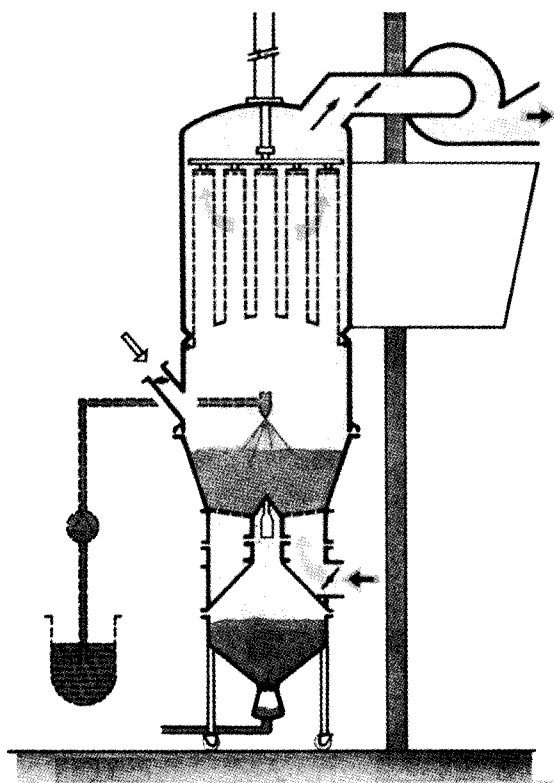


(b)

**Fig. 22** Continued

ing problems; because the process air and the product discharge follow the same path, assurance of cleanliness is always of prime concern.

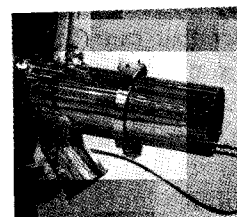
The desire to limit the processing area, and development of the overlap gill air distributor, mentioned earlier in the chapter, has prompted the consideration of the side discharge as an option. The product bowl is fitted with the discharge gate (Fig. 24). Most of the product, being free-flowing gran-



**Fig. 23** Fluid bed spray granulator with option of product discharge through the bottom (pneumatic or gravity). (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

ules, flows through the side discharge into a container. The remainder of the product is then discharged by manipulation of the airflow through the overlap gill air distributor. The discharged product can be pneumatically transported to an overhead bin, if dry milling of the granulation is desired.

This contained system for unloading the product helps isolate the operator from the product. The isolation feature also prevents the product from being contaminated by exposure to the working environment. Material-handling consideration must be thought of early in the equipment procurement process. For fluid bed processing—whether used as an integral part of high shear mixer—fluid bed dryer or as a granulating equipment option—production efficiency and eventual automation can be enhanced by considering these loading and unloading options.



*Side discharge system.*

*Side discharge (open).*



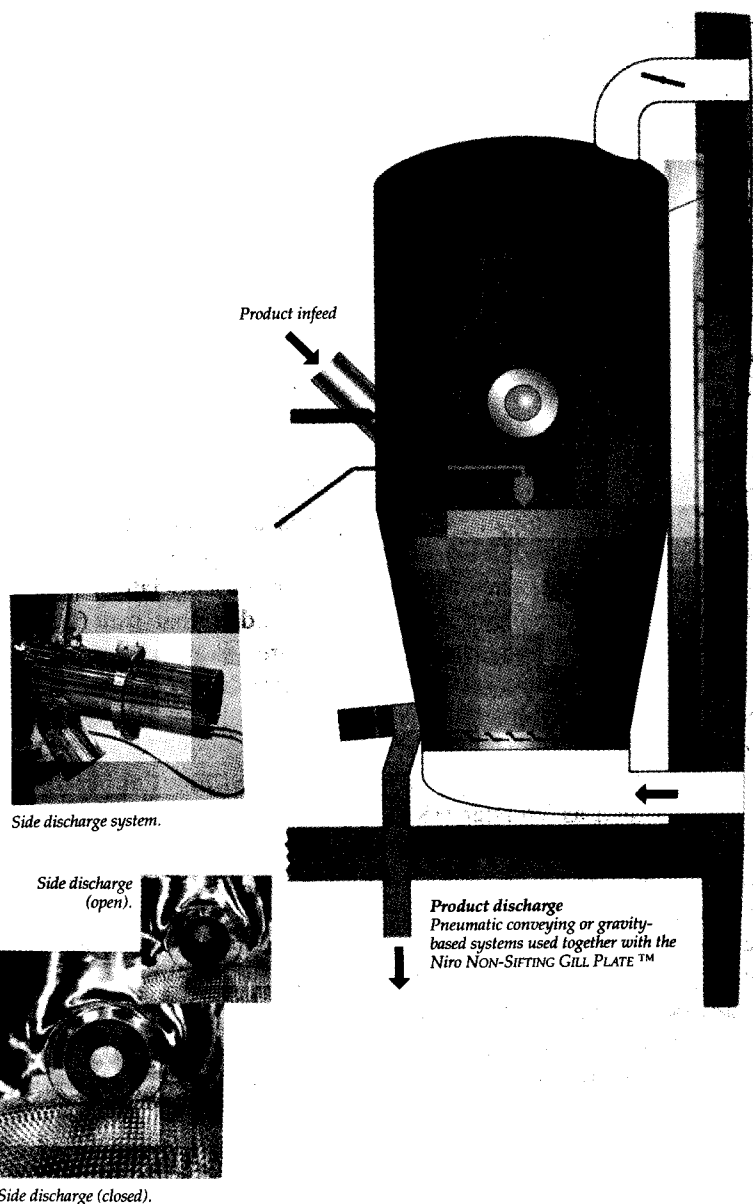
*Side discharge (closed).*

**Fig. 24** Product side discharge through overlap gill air distributor. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)



on of product discharge through the  
o Inc., Aeromatic-Fielder Division.)

a container. The remainder of the  
of the airflow through the over-  
duct can be pneumatically trans-  
f the granulation is desired.  
the product helps isolate the op-  
re also prevents the product from  
aking environment. Material-han-  
y in the equipment procurement  
r used as an integral part of high  
ulating equipment option—pro-  
can be enhanced by considering



**Fig. 24** Product side discharge showing closed and open discharge with overlap gill air distributor, (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

## XI. ADVANCES IN FLUID BED PROCESSORS

The fluid bed processor was used as an efficient way to dry a product because of suspension of particles in the hot airstream. However, the last 30 years of development in the pharmaceutical industry and the proliferation of the batch fluid bed-processing technology in other industries, such as food, polymer, detergent, and others, has provided the opportunity to use the batch fluid bed processor for granulation, coating of particles, and pelletization. The advances in the fluid bed can be attributed to several factors. The needs of formulators, the requirements of the regulators, and technological innovations from the manufacturers of this equipment are responsible for these advances. The result of these changes has provided units that are paint-free, modular, safer, in compliance with the cGMPs, and are capable of performing various processes that were not thought of before. The developments in this area have been recently reviewed by Parikh [98]. Among various advances, development of production units that can withstand 10-bar-pressure shock resistance is a very significant development. These units do not require a pressure relief duct, nor do they have the associated cleaning problems. Units are now equipped with the air handler that can provide designated humidity and dew point air throughout the year and at any geographic location. The fluid bed cleaning-in-place (cip) became a reality with the introduction of the overlap gill air distributors and the stainless steel cartridge filters described earlier in this chapter. The coating of the particles is carried out most frequently using a Wurster column (Fig. 25). In 1993, the design was modified as Wurster HS [116].

The Wurster process is the most popular method for coating particles. However, the technology has certain disadvantages, such as nozzle accessibility, prolonged process time, minimum volume requirement, and difficulty of loading and unloading. In 1995, to address these shortcomings of the Wurster system, the Precision Coater (Fig. 26), incorporating a modified air suspension technique, was introduced [99]. It was designed to allow removal of the nozzles for cleaning, faster process time because of the patented particle accelerator, good utilization of thermal and kinetic energies, and scalability from a single-column to a multicolumn setup.

Researchers have discussed the incorporation of a microwave generator into the laboratory fluid bed processor [125–126]. A fluid bed process using organic solvent requires inert gas, such as nitrogen, to replace the air used for fluidization. It is accompanied with the solvent recovery system. In 1989, a vacuum fluid bed system was presented by Luy et al. [127]. The main feature was the generation and sustaining of a fluidized bed under vacuum, thereby eliminating the use of inert gas. Several advantages are claimed by

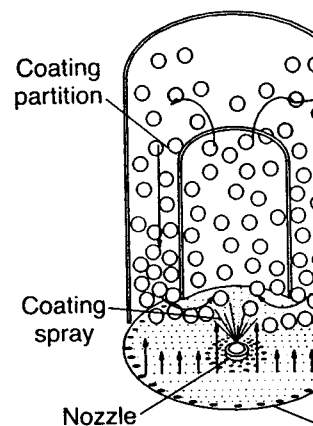


Fig. 25 Wurster Coater with

the authors, such as emissivity and an application for oxygen

There are three most common fluid bed agglomeration processes described in the following

### A. Granulation Endpoints

The endpoint of a fluid bed process has been determined by monitoring temperature, exhaust air temperature, the drying process is determined by experiments. Recently, infrared radiation has been used in a process called MM55 moisture analysis. Inc. (Concord MA; and Vaisala) that when infrared radiation (1000–3000 nm), is projected, it is selectively absorbed, and the emission of well-defined infrared wavelengths of the -OH groups in

## ESSORS

efficient way to dry a product be-  
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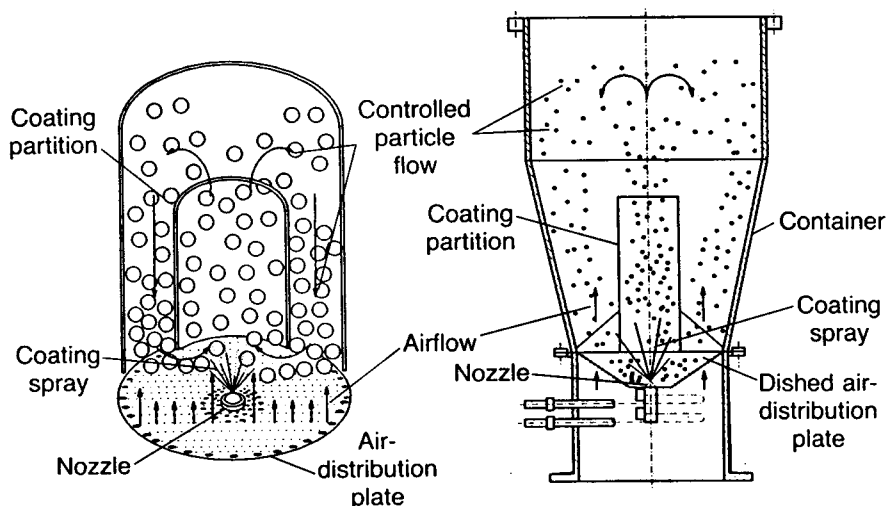


Fig. 25 Wurster Coater with two designs—a flat and a dished air distributor.

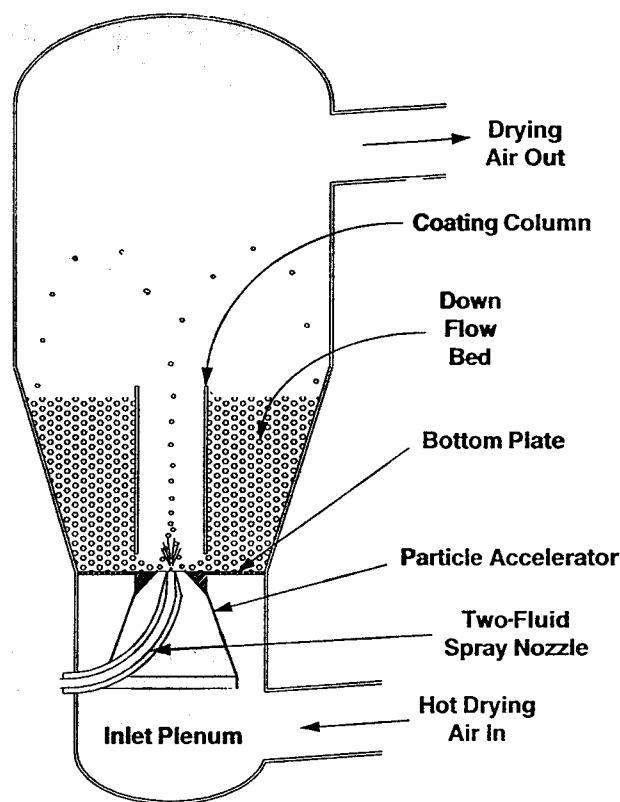
the authors, such as emission reduction, increased recovery rate of solvent, and an application for oxygen-sensitive materials.

There are three most significant developments that have affected the fluid bed agglomeration process. These three significant developments are described in the following.

### A. Granulation Endpoint

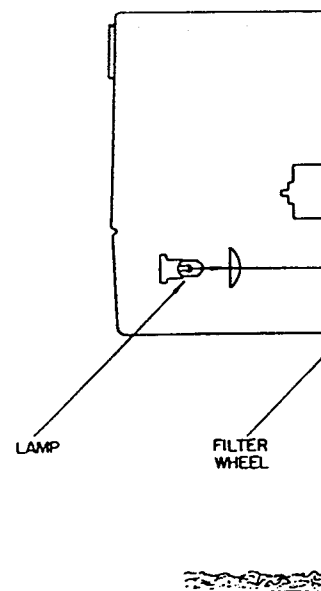
The endpoint of a fluid bed drying or granulating process has customarily been determined by monitoring the temperature of the exhaust gas stream. The reproducibility of the process is determined by a combination of bed temperature, exhaust air temperature, and drying time. The termination of the drying process is determined by plotting drying curves and by performing experiments. Recently, on-line moisture measurement using near infrared radiation has been used in the pharmaceutical industry. One such device, called MM55 moisture analyzer, is manufactured by Infrared Engineering, Inc. (Concord MA; and Wildberg, Germany). It is based on the principle that when infrared radiation, between the wavelengths of 1 and 3  $\mu\text{m}$  (1000–3000 nm), is projected onto a product containing moisture, some of it is selectively absorbed, whereas the remainder is scattered. The absorption, at well-defined infrared wavelengths, is accompanied by vibrational excitation of the -OH groups in the water. With the greater levels of moisture in





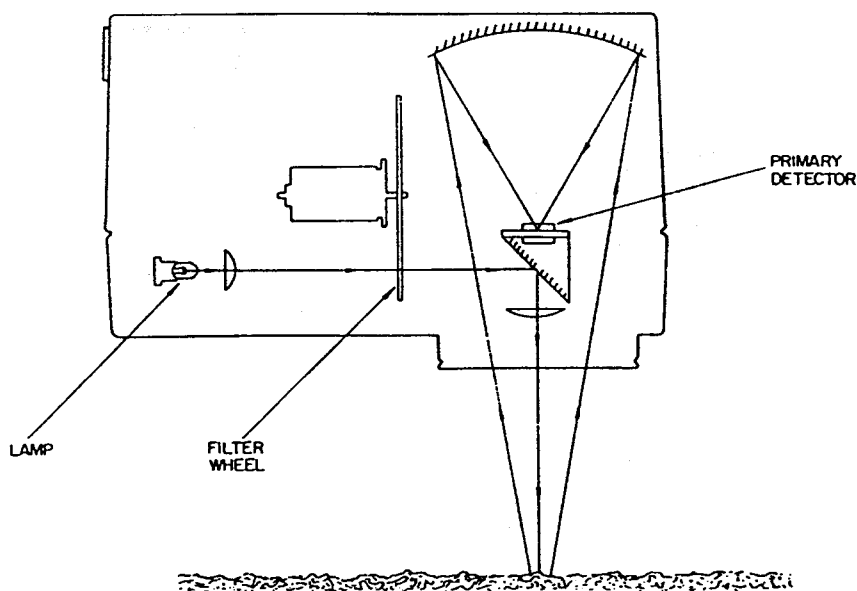
**Fig. 26** Schematic of a Precision Coater. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

the material, more absorption occurs at these wavelengths, with a corresponding reduction in the amount of diffused and reflected light. The measurement principle depends on the availability of a transducer to detect the changes in reflected intensity caused by absorption, and relates this to moisture content. By measuring the ratio of incident and transmitted energies and expressing it as a logarithm, a signal directly proportional to the moisture content is obtained. Figure 27 shows the schematic of MM55 unit. Radiation from the source, a quartz halogen lamp, is focused into a parallel beam, which is projected on the material to be measured. A rotating wheel, containing near infrared optical interference filters spinning in the optical path, provides the means of selecting narrow bands of infrared light at wavelengths corresponding to the "reference" and "absorption" wavelengths.



**Fig. 27** Near-infrared moisture measurement principles. (Courtesy of Infratec.)

Typically the wheel rotates continuously to provide a continuous measurement. The incident light on the product are both parallel and perpendicular. A portion of the scattered light is reflected by a mirror and focused onto a detector. The light is amplified and because both the incident and reflected light travel the same optical path, any change in the intensity will relate to absorption by the material. In this mode, such as absolute moisture measurement, the calibration station. To use the unit for batch fluid bed granulation-drying cycle, it is essential that the window is kept clear. This is achieved by coating the glass with a thin layer of material that interferes with the infrared light. The MM55 unit can be used for different materials as it changes during agglomeration. The near-infrared moisture measurement is a specially available instrument. The MM55 near-infrared unit is



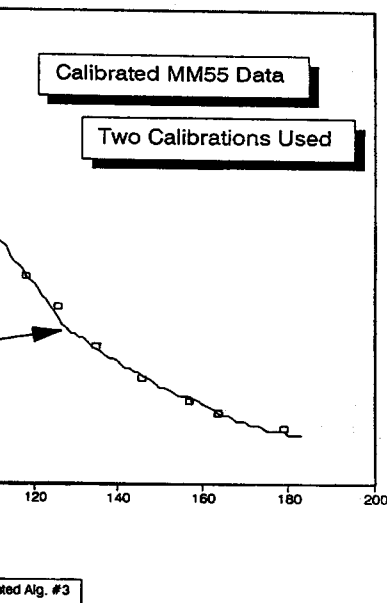
**Fig. 27** Near-infrared moisture measurement with MM55: schematics of operating principles. (Courtesy of Infrared Engineering, Inc., Concord MA.)

Typically the wheel rotates between 20 and 40 Hz, effectively providing a continuous measurement many times per second. The pulses of light arriving on the product are both partially scattered and partially absorbed. A proportion of the scattered light is collected by the sensing head's collecting mirror and focused onto a lead sulfide detector. The detected signals are amplified and because both the reference and absorption beams have taken the same optical path, any change in the value of the computed log ratio will relate to absorption by the component to be measured. The measurement mode, such as absolute moisture content, can be selected and recorded in the calibration station. To measure the moisture properly during the fluid bed granulation-drying cycle, the unit is mounted on the sight glass port. It is essential that the window has no powder sticking on it. This can be achieved by coating the glass with a clear nonstick material that will not interfere with the infrared pathway. Because this method is noninvasive, the unit can be used for different products. Efforts to measure product moisture as it changes during agglomeration and drying have been made by using infrared moisture measurement [100]. We have evaluated several commercially available instruments in our laboratories, and have found that the MM55 near-infrared unit is reproducible during the granulation of a phar-



granulation, several samples were moisture readings were taken by the laboratory moisture values were the unit, the manufacturer's rec- was provided with the unit. Dur- orated, until the moisture was 8%. % was performed and values were ch the response from a calibrated es were taken for LOD readings. nit were plotted. Figure 28 shows ere gathered using the moisture eeds to be further explored for a e fluid bed processor.

development of a rotary fluid bed were introduced by various man- ssed here. The 1972 patent [104]



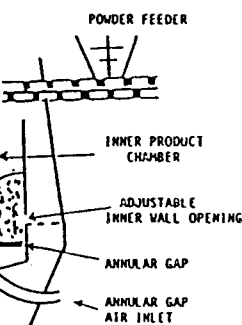
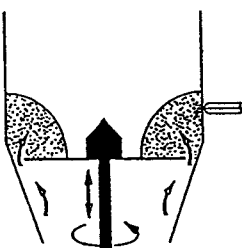
LOD data and MM55 data.

for the rotor technology was awarded for the equipment and coating of granular material. The subsequent patents [105,106] were rewarded for coating spherical granules. Advantages of rotary fluid bed processing to produce granules over the conventional top-spray granulation technique were reported by Jager and Bauer [107]. In this unit, the conventional air distributor is replaced by the rotating disk. The material to be granulated is loaded onto the rotating disk. The binder solution is added through the atomization nozzle, located tangentially to the wall of the bowl. The centrifugal force creates a dense, helical doughnut-shaped pattern. This type of motion is caused by the three directional forces.

The vertical movement is caused by the gap or slit air around the rotating disk, the gravitational force folds back the material to the center, and the centrifugal force, caused by the rotating disk, pushes the material away from the center. The granulation produced in the rotary fluid bed processor shows less porosity, when compared with the conventionally agglomerated product in the fluid bed processor. There are essentially two designs of these rotary fluid bed modules that are available: the single-chamber design, and the double-chamber design (Fig. 29). In the single-chamber design, the conventional air distributor is replaced by the rotating disk, which has a variable-sized slit opening between the bowl wall and the rotor disk. The fluidizing air enters the mixing zone in the bowl through the slit. The single-chamber design is manufactured by Glatt (W. Glatt GMBH, Binzen, Germany) as Glatt Rotor Granulator and by Freund (Freund Industrial Co., Ltd., Tokyo, Japan) as a Spir-a-Flow granulator. The Spir-a-Flow processing chamber consists of a rotor, through which heated air is introduced through 300- to 500- $\mu$ m openings in the rotor, as well as around the rotor's perimeter for fluidization of the product bed (Fig. 30).

The double-chamber design was patented and manufactured by Aeromatic-Fielder AG (Aeromatic-Fielder AG, Bubendorf, Switzerland) [117]. An inner stainless steel wall-encompassing area, called the forming zone, is surrounded by an annular drying zone. The forming zone has a rotating disk. The gap air around the rotating disk allows the disk's free movement. The stainless steel wall separating the forming zone and drying zone can be raised so that the rotating product transfers in the drying zone, through the gap created during the drying mode, between the stationary and movable wall. The process air fluidizes the product through the annular drying zone (Fig. 31). As the partially dried product reaches the upper boundary of the forming zone, particle velocity slows down, owing to the design of the unit, and particles fall back in the forming zone. These partially dried particles eventually go through the same path in a cyclic pattern until the desired moisture content is reached.





(a) single-chamber and (b) double-

designs does provide granules with uniformity, compared with the granulation using a rotary fluid bed process. The authors reported that the granules produced using a rotary fluid bed as a wet granulator showed uniformity for tablets, even when compared with conventional fluidized

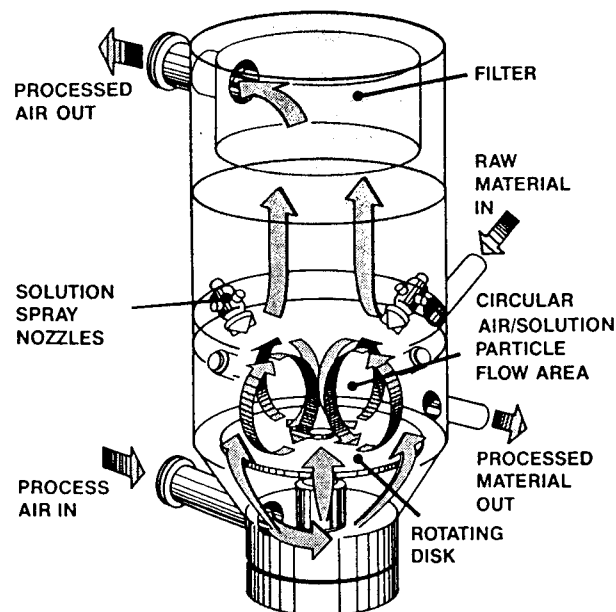
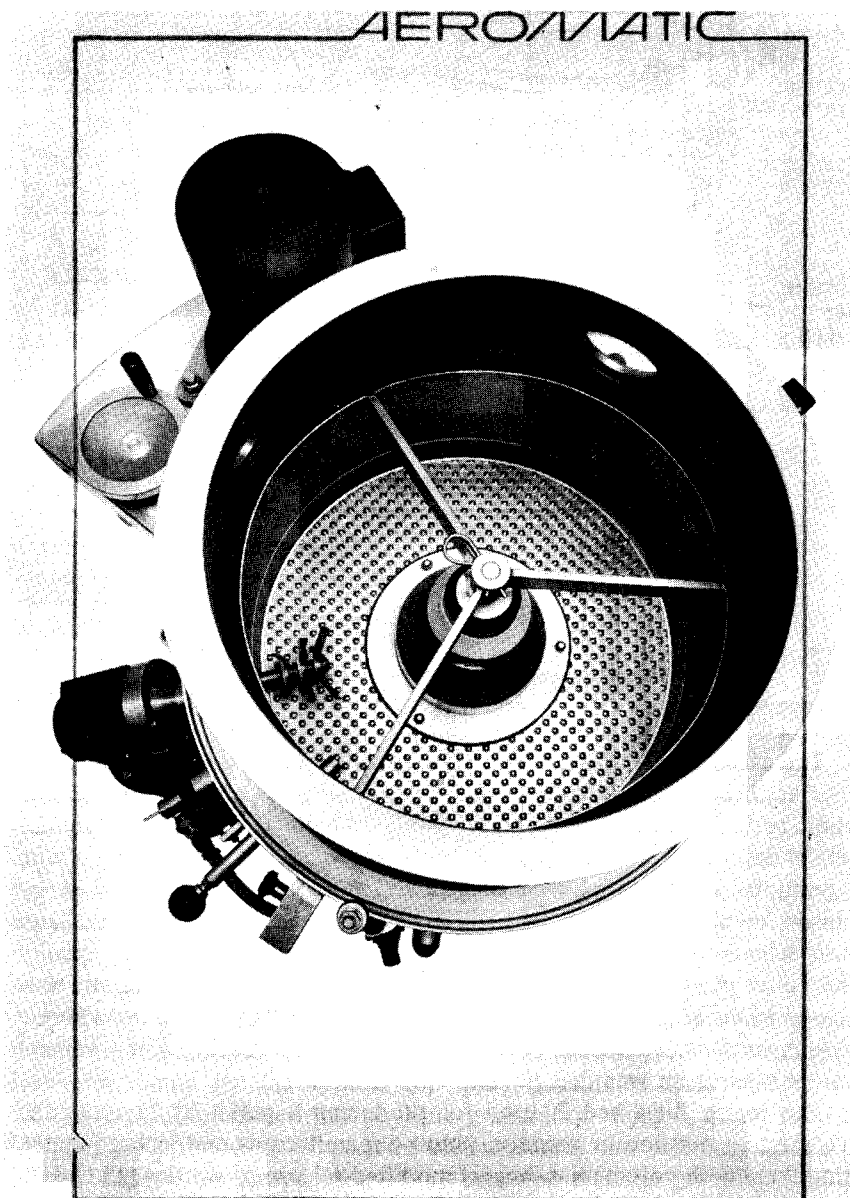


Fig. 30 Spir-a-Flow design. (From Vector Corp. brochure.)

The use of a rotary fluid bed to produce spherical granules for modified-release application has been reported by several authors. Rotary fluid bed technology is reviewed by Li et al. [109], and its usefulness to produce pellets is described. The comparison of the rotary fluid bed processing with the multiple step extrusion and spheronization has been reported by Robinson et al. [110]. The authors manufactured acceptable immediate-release acetaminophen pellets using both of these techniques. The quality of the pellet produced improved as the minimum quantity of product was increased in the rotary fluid bed processor. The advantages of using a single unit such as Rotoprocessor, over multiple unit process involving several pieces of equipment was described.

The rotary fluid bed is used for producing a pellet by layering the active drug suspension or solution onto nonpareil cores and, subsequently, coating them with polymers to impart modified-release properties [111]. Hillemann et al. [112] reported manufacture of immediate-release spheres of a poorly water-soluble drug in a rotary fluid bed by layering the active drug suspension onto nonpareil cores. These spheres were then overcoated with an ethylcellulose-HPMC hydroalcoholic solution in the same unit, eliminating the need for additional process and handling steps. Iyer et al. eval-

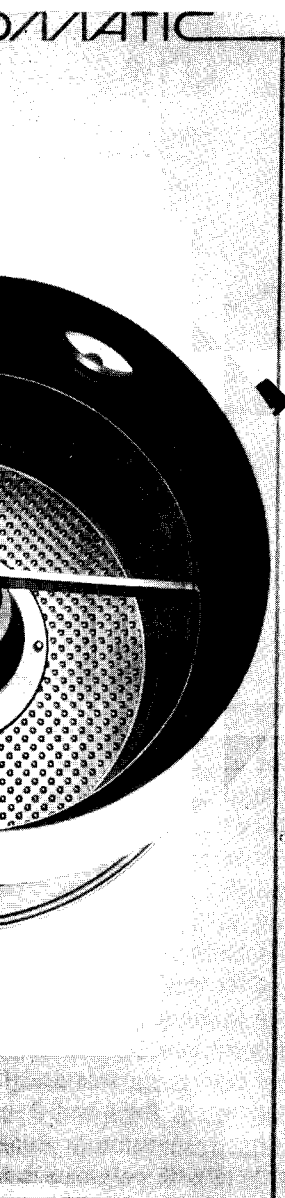


**Fig. 31** Rotaprocessor design showing two chambers with the annular drying zone.  
(Courtesy of Niro Inc., Aeromatic-Fielder Division.)

uated layering of aqueous with different binders [113]. The Wurster processor and the Wurster Co. processor as equipment not Layering of the powder promoted by various manufacturers received a patent for such advantages of layering a liquid, thus making this application of this process

### C. Clean-in-Place Des

The cleaning of process products has been discussed in a fluid bed processor, cleaning in cause of two components: with the retention screen. the air distributor with sand unit, disassembled, and cleaning is labor-intensive team, 8–10 h to clean the cleaning has been the difficult was granted for a true clean of overlap gill air distributor capability of cleaning all 32a shows a stainless steel system for the fluid bed. can be performed without easy to validate the clean integrated into the normal conveyor washer for the processor, spray filter cleaning system, the cartridge-cleaning system during the cleaning cycle, annular nozzles around the are cleaned as the cartridge rotates the cartridges. At the tower sprays liquid through cartridge. The lower plenum nozzle placed in the lower



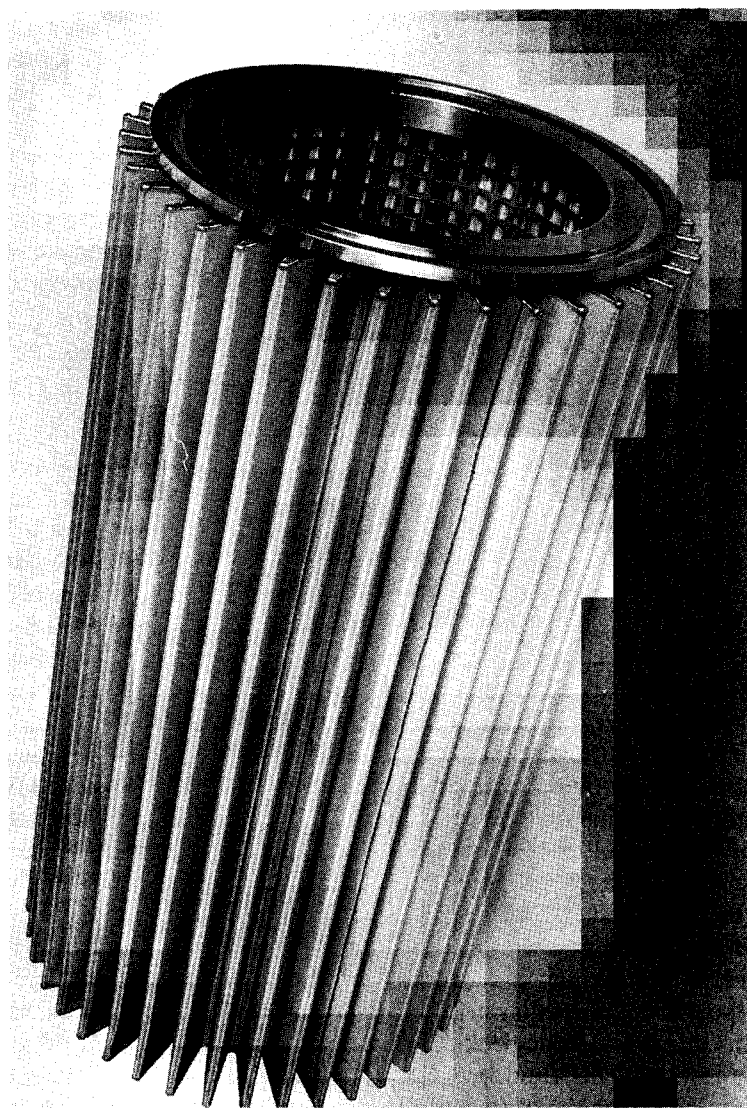
members with the annular drying zone.  
(on.)

uated layering of aqueous solution of phenylpropanolamine hydrochloride with different binders [113]. The layered beads were coated in the Rotoprocessor and the Wurster Coater to compare the usefulness of the Rotoprocessor as equipment not only to produce pellets, but also to coat them. Layering of the powder onto the pellets in a rotary fluid bed has been promoted by various manufacturers of the equipment. In 1992, Jones et al. received a patent for such a process [115]. The process claims to have advantages of layering a drug substance with relatively small amount of liquid, thus making this layering process more efficient. The commercial application of this process has not been reported in the literature.

### C. Clean-in-Place Design

The cleaning of process equipment used for different pharmaceutical products has been discussed extensively in the literature [118–124]. For fluid bed processor, cleaning in place (cip) has not been possible until now because of two components: namely, the filter bags and the air distributor plate with the retention screen. To clean fluid bed equipment, the filter bags and the air distributor with sandwiched construction has to be removed from the unit, disassembled, and cleaned. Because of this handling, the fluid bed cleaning is labor-intensive and time-consuming. It can take a two-person team, 8–10 h to clean the fluid bed. The other disadvantage of manual cleaning has been the difficulty of assuring reproducibility. In 1993, a patent was granted for a true clean-in-place (cip) system [103]. The introduction of overlap gill air distributors and stainless steel cartridges has provided the capability of cleaning all the components of the fluid bed in place. Figure 32a shows a stainless steel cartridge filter, and Fig. 32b shows a typical cip system for the fluid bed. Because this system can be automated, cleaning can be performed without operator intervention. This automation makes it easy to validate the cleaning procedure. The control package can be integrated into the normal control system of the processor. By providing a tank washer for the processor, strategically placed cleaning nozzles, and cartridge-filter cleaning system, the fluid bed can be cleaned in place. The unique cartridge-cleaning system involves cartridges that can be raised and lowered during the cleaning cycle, a spray nozzle at the top of the cartridge, and annular nozzles around the cartridge tower base. The pleats of the cartridge are cleaned as the cartridges move up and down, and the force of the spray rotates the cartridges. At the same time, the nozzle at the top of the cartridge tower sprays liquid through the cartridge filter media and backflushes the cartridge. The lower plenum and overlap gill air distributor is cleaned by a nozzle placed in the lower plenum. The cleaning regimen is determined in





(a)

**Fig. 32** (a) A pleated stainless steel cartridge for cip; (b) A validatable cip system for cleaning the fluid bed. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

FILTER  
BLOW BACK  
NOZZLE

FILTER  
CARTRIDGE

PRODUCT  
INFEED  
SYSTEM

(PRODUCT)  
SIDE DISCHARGE  
SYSTEM

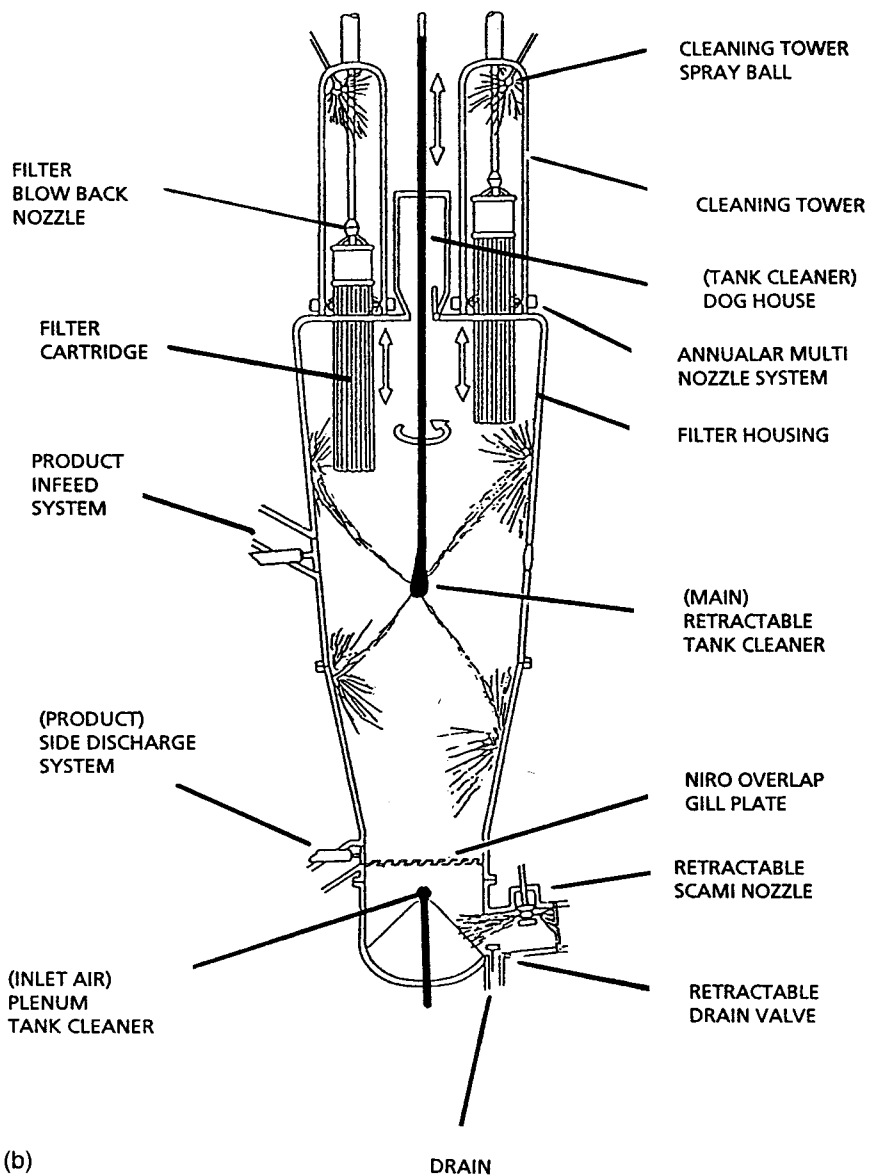
(INLET AIR)  
PLENUM  
TANK CLEANER

(b)

**Fig. 32** Continued



or cip; (b) A validatable cip system  
, Aeromatic-Fielder Division.)



(b)

Fig. 32 Continued

the early stages of cleaning method development and are programmed to provide consistency in cleaning.

## XII. CONTEMPORARY TRENDS

The fluid bed technology is used for drying, agglomerating, coating, and pelletization. The trend in the industry is toward integrating various steps currently used to produce the solid dosage products. In an attempt to minimize the number of steps involved, fluid bed granulation and drying is increasingly planned in the following three ways.

1. Fluid bed processor for granulation and drying
2. Integration of a high shear mixer and a fluid bed dryer
3. Integration of high shear mixer with fluid bed dryer for containment of potent compounds

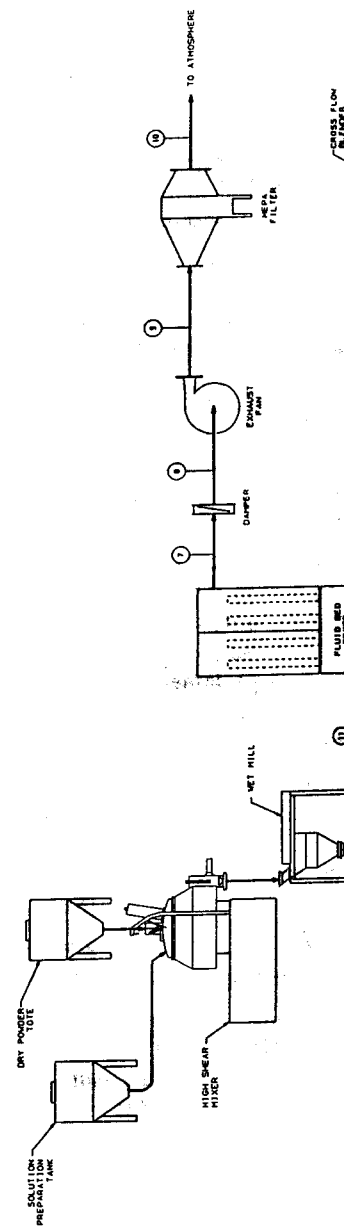
### A. Granulation and Drying in a Single Unit

To minimize material handling steps, the fluid bed units are loaded by gravity or by vacuum, as described previously. Discharge of the product from the unit is accomplished by either side or bottom discharge, employing a pneumatic transport system. The cleaning-in-place of such a unit can be accomplished by using stainless steel cartridge filters and an overlap gill air distributor if desired.

### B. Integration of a High Shear Mixer with a Fluid Bed Dryer

Figure 33 is a typical integrated system in which containment is considered for controlling dust and cross-contamination. When these two unit operations are integrated as a single unit, several points must be considered. The following is the list of some of the questions readers may want to consider:

1. Engineering layout and the footprint, ceiling height requirements.
2. How will the high shear mixer be loaded—by gravity, vacuum, or manually?
3. How will the binder solution be prepared and delivered to the mixer?
4. How will the granulation endpoint be determined and reproduced?
5. How will the discharge from the high shear mixer be accomplished?



opment and are programmed to

ing, agglomerating, coating, and  
toward integrating various steps  
products. In an attempt to min-  
bed granulation and drying is  
ways.

on and drying  
and a fluid bed dryer  
with fluid bed dryer for contain-

### e Unit

id bed units are loaded by grav-  
Discharge of the product from  
bottom discharge, employing a  
in-place of such a unit can be  
lge filters and an overlap gill air

### with a Fluid Bed

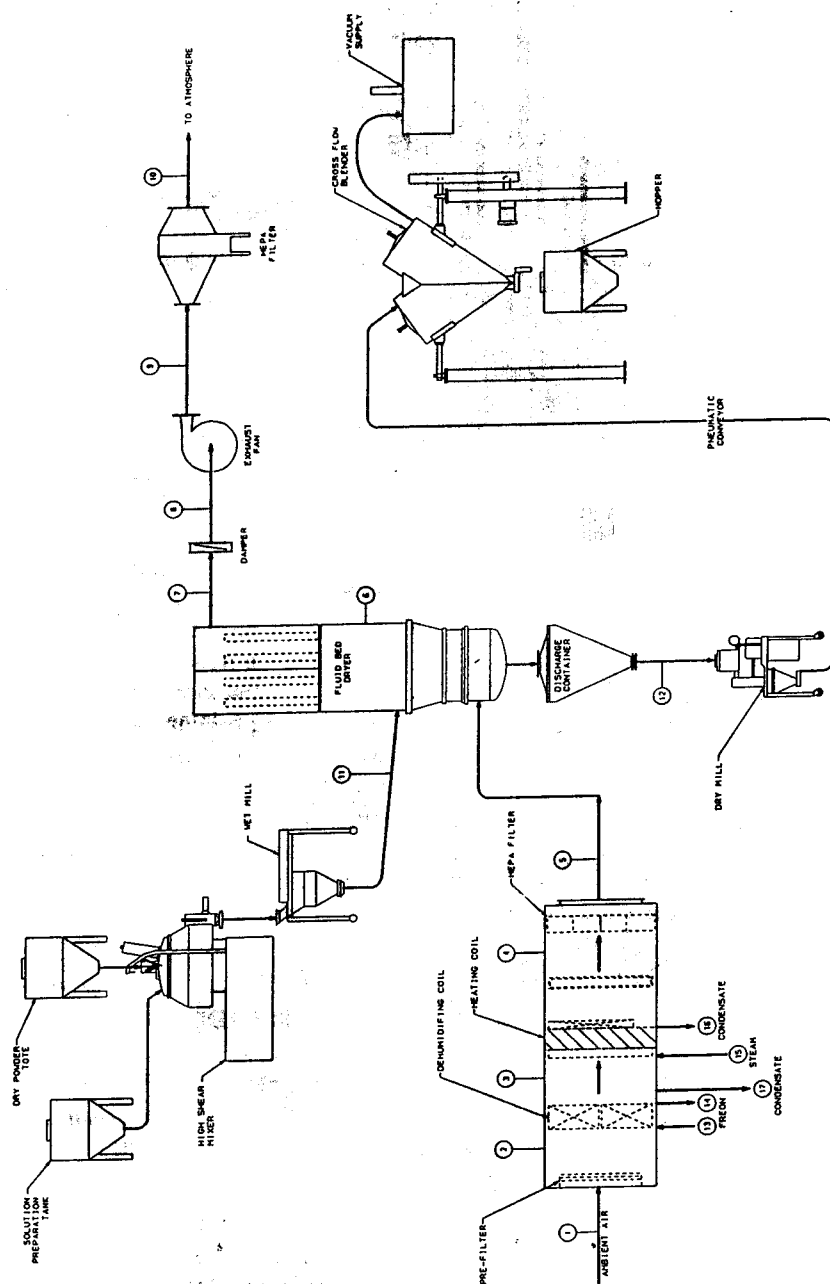
which containment is considered  
When these two unit operations  
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readers may want to consider:

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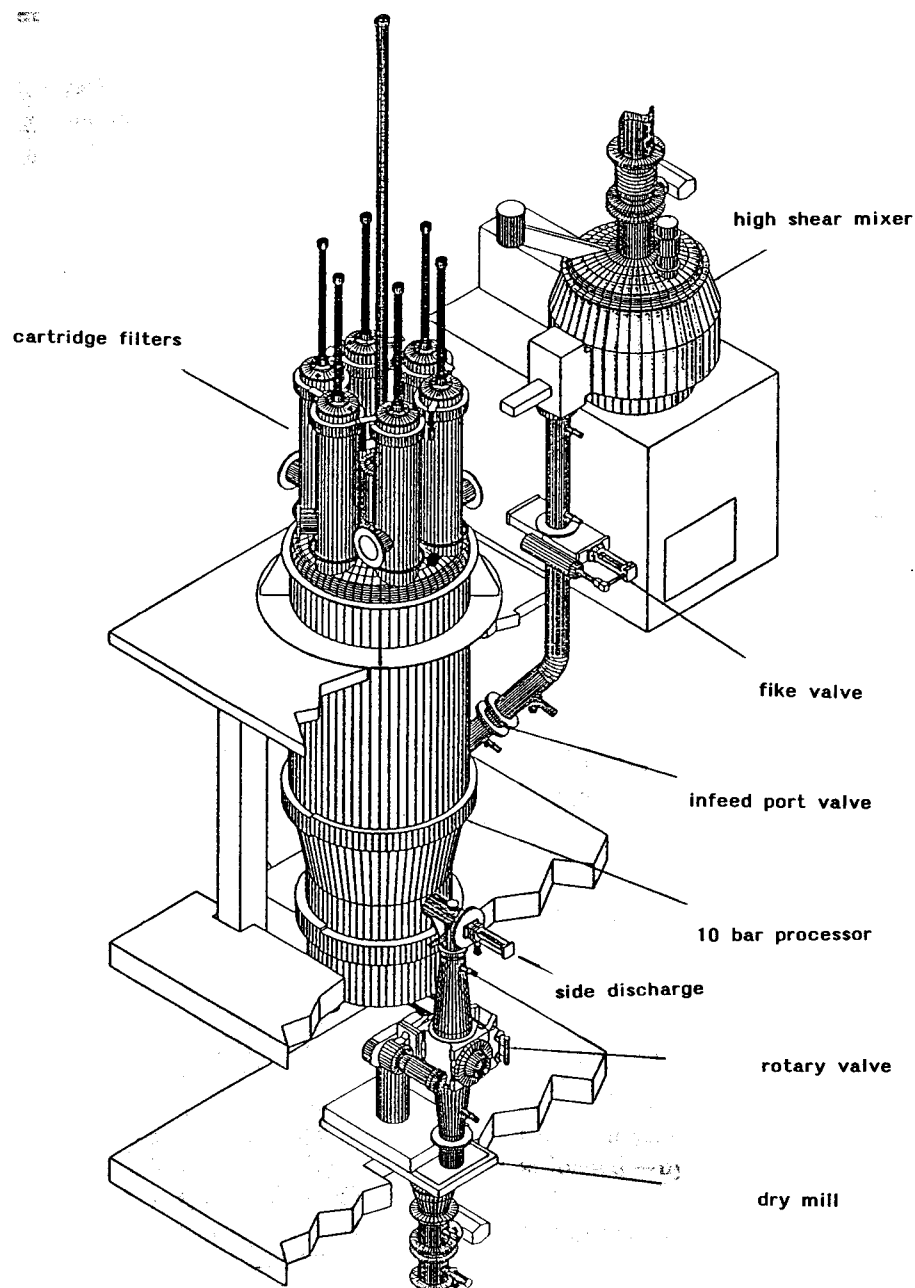
be prepared and delivered to the

oint be determined and repro-

the high shear mixer be accom-



**Fig. 33** High shear mixer and fluid bed dryer as an integrated unit operation. (Courtesy of Niro Inc., Aeromatic-Felder Division.)



**Fig. 34** Integrated system for processing potent compounds using a high shear granulator and fluid bed dryer with cartridge filters, overlap gill air distributor, and cip cleaning system. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

6. Are the process established and cess?
7. How will the p handled? Does i
8. Is this system de products?
9. How will this sy
10. Will the control or by an integra

### C. Integration of a High for Containment of

For the potent compound p fluid bed drying, all the fore the operator safety, special tems, and cleaning-in-place can be dedicated for a single a potent compound is proce erating personnel do not ha drying steps. Such a system of time for process and cle

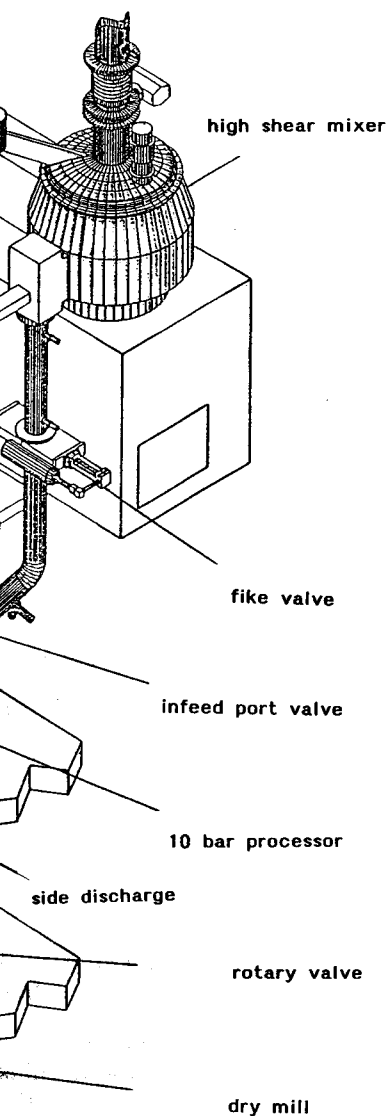
The fluid bed process, an understanding of the imp especially of a drug subst selected process, establishm acterization of the finished is equally important that th lose sight of the fact that th to go on the production flo

### ACKNOWLEDGMENTS

The authors thank Mr. Dan ski, and Ms. Patti Basil of help in the preparation of t

### REFERENCES

1. D Kunii, O Lvenspiel. Sons, 1968.



6. Are the process parameters for granulation and fluid bed drying established and are they reproducible, indicating a robust process?
7. How will the product discharged from the fluid bed dryer be handled? Does it require sizing or blending with the lubricants?
8. Is this system dedicated for a single product, or used for multiple products?
9. How will this system be cleaned?
10. Will the control of a process be done individually for each unit, or by an integrated control system?

### C. Integration of a High Shear Mixer with a Fluid Bed Dryer for Containment of Potent Compounds

For the potent compound processing requiring high shear granulation and fluid bed drying, all the foregoing questions must be considered. In addition, the operator safety, special sampling valves, isolated room air-handling systems, and cleaning-in-place must be considered. Such an integrated system can be dedicated for a single product. Figure 34 shows a system in which a potent compound is processed. After the raw materials are dispensed, operating personnel do not have to handle the product during the granulation-drying steps. Such a system is costly and does require an enormous amount of time for process and cleaning validation.

The fluid bed process, similar to other granulation techniques, requires an understanding of the importance of characterization of the raw materials, especially of a drug substance, the process equipment, limitations of the selected process, establishment of in-process control specifications, characterization of the finished product, and cleaning and process validation. It is equally important that the formulation and development scientists do not lose sight of the fact that the process being developed must be robust enough to go on the production floor.

### ACKNOWLEDGMENTS

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### REFERENCES

1. D Kunii, O Lvenspiel. *Fluidization Engineering*. New York: John Wiley & Sons, 1968.

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romatic-Fielder Division.)

2. DE Wurster. *J Am Pharm Assoc Sci Ed* 49:82, 1960.
3. DE Wurster. *J Am Pharm Assoc Sci Ed* 48:451-454, 1959.
4. MW Scott, HA Liberman, AS Rankell, JV Battista. *J Pharm Sci* 53:314-319, 1964.
5. AS Rankell, MW Scott, HA Liberman, FS Chow, JV Battista. *J Pharm Sci* 53:320, 1964.
6. S Contini, K Atasoy. *Pharm Ind* 28:144-146, 1966.
7. G Wolf. *Drugs Made Germ* 11:172-180, 1968.
8. T Liske, W Mobus. The manufacture and comparative aspects of fluidized layer spray granulation. *Drugs Made Germ* 11:182-189, 1968.
9. PJ Sherrington, R Oliver. Granulation. In: AS Goldberg, ed. *Power Science and Technology*. London: Heyden, 1981.
10. WB Pietch. In: ME Fayed, L Otten, eds. *Handbook of Powder Science and Technology*. New York: van Nostrand Reinhold, 1984.
11. Hersey JA. Fluidized bed technology—an overview. *Int J Pharm Technol Prod Manuf* 2(3), 1981.
12. WJ Thiel. The theory of fluidization and application to the industrial processing of pharmaceutical products. *Int J Pharm Technol Prod Manuf* 2(4): 5-8, 1981.
13. WJ Thiel. Solids mixing in gas fluidized beds. *Int J Pharm Technol Prod Manuf* 2(4):9-12, 1981.
14. H Littman. An overview of flow in fluidized beds. *Pharm Technol* 9(3):48, 1985.
15. AB Whitehead. In: JF Davidson and D Harrison, eds. *Fluidization*, Academic Press, 1971, Chapter 19, p. 781.
16. MJ Story. Granulation and film coating in the fluidized bed. *Pharm Technol* 2(4):19-23, 1981.
17. MJ Aulton, M Banks. Fluidized bed granulation, factors influencing the quality of the product. *Int J Pharm Technol and Prod Manuf* 2(4):24-29, 1981.
18. W Kulling, Simon. Fluid bed technology applied to pharmaceuticals. *Pharm Technol* 4(3):79-83, 1980.
19. A Gomezplata, AM Kugelman. Processing systems. In: M Marchello, A Gomezplata, eds. *Gas-Solid Handling in the Process Industries*, Chemical Processing and Engineering; Vol. 8. New York: Marcel Dekker, 1976.
20. DM Parikh. Airflow in batch fluid-bed processing. *Pharm Technol* 15:100-110, 1991.
21. PN Row, et al. *Trans Inst Chem Eng* 32T:271, 1965.
22. L Davis, et al. *Trans Inst Chem Eng* 44T:293, 1966.
23. VI Gorrodnichev, et al. *Pharm Chem J (USSR) (English translation)* 8:298, 1974.
24. WJ Thiel. The theory of fluidization and application to the industrial processing of pharmaceutical products. *Int J Pharm Technol Prod Manuf* 2(4): 5-8, 1981.
25. Kirk-Othmer. Fluidization. In: *Encyclopedia of Chemical Technology*. vol 10, 3rd ed. New York: Wiley-Interscience, 1980, 548-581.
26. DM Newitt, JM Conway. granulation. *Int J Pharm*
27. PC Record. A review of Technol Prod Manuf 1:3
28. Rumpf. Agglomeration.
29. T Schaefer, O Worts. Co angle, nozzle height and tion. *Arch Pharm Chem*
30. PJ Smith, AW Nienow. C
31. ME Aulton, M Banks. In
32. A Maroglou, AW Nienow Canada: Iron & Steel So
33. A Maroglou, AW Nienow plication to tungsten carb
34. WL McCabe, JC Smith. M McGraw-Hill, 1956.
35. DW Green, ed. Perry's M McGraw-Hill, 1984.
36. RS Rankell, HA Liberman tice of Industrial Pharma
37. T Schaefer, O Worts. Co air temperature, and liqu Control of moisture con Chem Sci Ed 6:1-13, 19
38. U Thurn. Dissertation 4 rich, 1970.
39. T Liske, W Mobus. Dru
40. T Schaefer, O Worts. Co angle, nozzle height and tion. *Arch Pharm Chem*
41. T Schaefer, O Worts. Co granule growth. *Arch PH*
42. Z Ormos, K Pataki. Hur
43. Z Ormos, K Pataki. Hur
44. M Banks, PhD dissertati
45. MJ Galmen, W Greer. I ternational Conference,
46. ME Aulton. Fluid Tech Conference, paper 3, Po
47. M Veillard, et al. *Int J P*
48. PP Georgakopoulos, et a
49. JC Jinot, et al. *STP Pha*
50. A Shinoda, et al. *Yakuz*
51. ME Aulton, et al. *J Pha*
52. G Schepky. *Acta Pharm*

- d 49:82, 1960.
- d 48:451-454, 1959.
- JV Battista. *J Pharm Sci* 53:314-319, 1964.
- FS Chow, JV Battista. *J Pharm Sci* 55:141-146, 1966.
- 0, 1968.
- and comparative aspects of fluidized bed granulation. *Pharm Technol* 11:182-189, 1968.
- In: AS Goldberg, ed. *Power Science and Technology*. New York: Marcel Dekker, 1970.
- s. *Handbook of Powder Science and Technology*. Reinhold, 1984.
- an overview. *Int J Pharm Technol Prod Manuf* 2(4):24-29, 1981.
- and application to the industrial process. *Int J Pharm Technol Prod Manuf* 2(4):24-29, 1981.
- ed beds. *Int J Pharm Technol Prod Manuf* 2(4):24-29, 1981.
- idized beds. *Pharm Technol* 9(3):48, 1985.
- Harrison, eds. *Fluidization*, Academic Press, 1986.
- in the fluidized bed. *Pharm Technol Prod Manuf* 2(4):24-29, 1981.
- ulation, factors influencing the quality of granulation. *Pharm Technol* 15:100-105, 1991.
- and Prod Manuf 2(4):24-29, 1981.
- y applied to pharmaceuticals. *Pharm Technol* 15:100-105, 1991.
- ising systems. In: M Marchello, A Biondi, eds. *Fluidization in the Process Industries*, Chemical Engineering Series, Marcel Dekker, New York: Marcel Dekker, 1976.
- rocessing. *Pharm Technol* 15:100-105, 1991.
- T:271, 1965.
- T:293, 1966.
- (USSR) (English translation) 8:298, 1966.
- and application to the industrial process. *Int J Pharm Technol Prod Manuf* 2(4):24-29, 1981.
- edia of Chemical Technology. vol 10, 1980, 548-581.
26. DM Newitt, JM Conway-Jones. A contribution to the theory and practice of granulation. *Int J Pharm Technol Prod Manuf* 36:422, 1958.
27. PC Record. A review of pharmaceutical granulation technology. *Int J Pharm Technol Prod Manuf* 1:32, 1980.
28. Rumpf. Agglomeration. In: W Krepper, ed. New York: Interscience, 1962.
29. T Schaefer, O Worts. Control of fluidized bed granulation I: effects of spray angle, nozzle height and starting materials on granule size and size distribution. *Arch Pharm Chem Sci Ed* 5:51-60, 1977.
30. PJ Smith, AW Nienow. *Chem Eng Sci* 38:1223-1231; 1323-1240, 1983.
31. ME Aulton, M Banks. *Int J Pharm Technol Prod Manuf* 2:24-29, 1981.
32. A Maroglou, AW Nienow. Fourth Symposium on Agglomeration. Toronto, Canada: Iron & Steel Society Inc., June 1985; 465-470.
33. A Maroglou, AW Nienow. Fluidized bed granulation technology and its application to tungsten carbide. *Powder Metallurgy* 29(4):291-295, 1986.
34. WL McCabe, JC Smith. *Unit Operations of Chemical Engineering*. New York: McGraw-Hill, 1956.
35. DW Green, ed. *Perry's Chemical Engineer's Handbook*, sec 20. New York: McGraw-Hill, 1984.
36. RS Rankell, HA Liberman, RF Schiffman. *Drying*. In: *The Theory and Practice of Industrial Pharmacy*, 3rd ed. Philadelphia: Lea & Feabiger, 1986.
37. T Schaefer, O Worts. Control of fluidized granulation III: effects of the inlet air temperature, and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. *Arch Pharm Chem Sci Ed* 6:1-13, 1978.
38. U Thurn. Dissertation 4511, Eidgenossischen Technischen Hochschule, Zurich, 1970.
39. T Liske, W Mobus. *Drugs Made Germ* 11:182-189, 1968.
40. T Schaefer, O Worts. Control of fluidized bed granulation. I. Effects of spray angle, nozzle height and starting materials on granule size and size distribution. *Arch Pharm Chem Sci Ed* 5:51-60, 1977.
41. T Schaefer, O Worts. Control of fluidized bed granulation V. Factors affecting granule growth. *Arch Pharm Chem Sci Ed* 6:69-82, 1978.
42. Z Ormos, K Pataki. *Hung J Ind Chem* 7:89-103, 1979.
43. Z Ormos, K Pataki. *Hung J Ind Chem* 7:105-117, 1979.
44. M Banks, PhD dissertation. C.N.A.A. Leicester Polytechnic, 1981.
45. MJ Galmen, W Greer. *Fluid Technology Pharmaceutical Manufacturing International Conference*, paper 2, Powder Advisory Center, London, 1982.
46. ME Aulton. *Fluid Technology Pharmaceutical Manufacturing International Conference*, paper 3, Powder Advisory Center, London, 1982.
47. M Veillard, et al. *Int J Pharm Technol Prod Manuf* 3:100-107, 1982.
48. PP Georgakopoulos, et al. *Pharmazie* 38:240-243, 1983.
49. JC Jinot, et al. *STP Pharma* 2(13):126-131, 1986.
50. A Shinoda, et al. *Yakuzaigaku* 36:83-88, 1976.
51. ME Aulton, et al. *J Pharm Pharmacol Suppl* 59 pp, 1977.
52. G Schepky. *Acta Pharm Technol* 24:185-212, 1978.



53. ME Aulton, et al. Proceedings International Conference on Powder Technology in Pharmacy. Powder Advisory Center, Basel, Switzerland, June 1979.
54. EL Kocova, S Arini, et al. *Drugs Made Germ* 26:205-211, 1983.
55. WL Davies, WT Gloor. *J Pharm Sci* 61:618-622, 1972.
56. M Rouiller, et al. *Acta Pharm Technol* 21:129-138, 1975.
57. T Schaefer, O Worts. Control of fluidized bed granulation II, estimation of droplet size of atomized binder solution. *Arch Pharm Chem Sci Ed* 5:178-193, 1977.
58. Z Ormos, et al. *Hung J Ind Chem* 7:131-140, 1979.
59. Z Ormos, et al. *Hung J Ind Chem* 7:141-151, 1979.
60. Z Ormos, et al. *Hung J Ind Chem* 7:153-163, 1979.
61. Z Ormos, et al. *Hung J Ind Chem* 7:221-235, 1979.
62. S Kocova El-Arini. *Pharm Ind* 43:674-679, 1981.
63. KF Jager, KH Bauer. *Acta Pharm Technol* 30:85-92, 1984.
64. ATI Nouh. *Pharm Ind* 48:670-673, 1986.
65. H Alkan, et al. *Doga Tu J Med Pharm* 11:1-7, 1987.
66. A Bank, et al. *Proc Conf Appl Phys Chem* 2:687-692, 1971.
67. WL Davies, WT Gloor. *J Pharm Sci* 62:170-172, 1973.
68. Z Ormos, et al. *Hung J Ind Chem* 1:307-328, 1973.
69. Z Ormos, et al. *Hung J Ind Chem* 1:463-474, 1973.
70. MCR Johnson, et al. *J Pharm Pharmacol Suppl* 80 pp, 1975.
71. T Schaefer, O Worts. Control of fluidized bed granulation IV, effects of binder solution and atomization on granule size and size distribution. *Arch Pharm Chem Sci Ed* 6:14-25, 1978.
72. ME Aulton, et al. *Manuf Chem Aerosol News* 12:50-56, 1978.
73. VI Gorodnichev, et al. *Pharm Chem J (USSR)* 14(10):72-77, 1980.
74. GC Ceschel, et al. *Farm Ed Prat* 36:281-293, 1981.
75. G Rangnarsson, et al. *Int J Pharm* 12:163-171, 1982.
76. M Meshali, HM El-Banna, H El-Sabbagh. *Pharmazie* 38:323-325, 1983.
77. R Hajdu, Z Ormos. *Hung J Ind Chem* 12:425-430, 1983.
78. A Devay, et al. *Acta Pharm Technol* 30:239-242, 1984.
79. MH Alkan, A Yuksel. *Drug Dev Ind Pharm* 12:1529-1543, 1986.
80. J Hontz. Assessment of selected formulation and processing variables in fluid bed granulation. PhD dissertation. University of Maryland at Baltimore, 1987; Diss. Abstr Int (6):1655-B, 1987.
81. LSC Wan, KS Lim. *STP Pharm* 4:560-571, 1988.
82. LSC Wan, KS Lim. *STP Pharm* 5:244-250, 1989.
83. AY Gore, DW McFarland, NH Batuyios. Fluid bed granulation: factors affecting the process in laboratory development and production scale-up. *Pharm Technol* 9:114, 1985.
84. Niro Inc., Aeromatic-Fielder Division. Unpublished data.
85. WL Davies, WT Gloor Jr. Batch production of pharmaceutical granulation in fluidized bed I: effects of process variables on physical properties of final granulation. *J Pharm Sci* 60:1869-1974, 1971.
86. TC Dahl, AP Bormeth. Naproxen controlled release matrix tablets: fluid bed granulation feasibility. *Drug Dev Ind Pharm* 16:581-590, 1990.
87. SC Wan Lucy, PWS Her. dose drug in granules. I.
88. F Higashide, Y Miki, Y uniformity on particle size. 1205, 1985.
89. WL Davies, WT Gloor. fluidized bed II: effects of granulations and compressed.
90. WL Davies, WT Gloor. fluidized bed III: binder d.
91. FA Rawley. Effects of the of granulation. *Pharm T*
92. JA Bonck. Spray granulation 1993.
93. AAPS/FDA. Scale-up of
94. FDA. Immediate release changes: chemistry, manufacturing in-vivo bioequivalence Evaluation and Research
95. DM Jones. Factors to consider 50, 1985.
96. EJ Simon. Fluid bed production national Powder Techn PowTech Harrogate, UK
97. W Kulling. Method and for use in a process based March 27, 1979.
98. DM Parikh. Fluid bed production Year Book. Pharm
99. International patent WO
100. VL Henkel, H Henning. *Pharm Ind* 54:1047-10
101. US patent 5,392,531, 19
102. Japanese patent applicat
103. Swiss patent 0176/93, 0572356A1.
104. US patent, 3,671,296, J
105. US patent, 4,034,126, J
106. US patent, 4,542,043, S
107. KF Jäger, KH Bauer. Eff fluidized-bed granulator
108. Türkoglu, Murat, He M wet granulation equipment
109. Li Shun Por, CR Kow. croencapsulation technology 376, 1988.

- International Conference on Powder Technology, Basel, Switzerland, June 1979.
- Germ 26:205-211, 1983.
- 18-622, 1972.
- :129-138, 1975.
- Fluid bed granulation II, estimation of Arch Pharm Chem Sci Ed 5:178-140, 1979.
- 151, 1979.
- 163, 1979.
- 235, 1979.
- 79, 1981.
- 1 30:85-92, 1984.
- :1-7, 1987.
- n 2:687-692, 1971.
- 70-172, 1973.
- 328, 1973.
- 474, 1973.
- Suppl 80 pp, 1975.
- Fluid bed granulation IV, effects of binder and size distribution. Arch Pharm News 12:50-56, 1978.
- SSR) 14(10):72-77, 1980.
- 293, 1981.
- 171, 1982.
- . Pharmazie 38:323-325, 1983.
- :425-430, 1983.
- 39-242, 1984.
- rm 12:1529-1543, 1986.
- on and processing variables in fluid ity of Maryland at Baltimore, 1987; 71, 1988.
- 50, 1989.
- Fluid bed granulation: factors affecting and production scale-up. Pharm unpublished data.
- on of pharmaceutical granulation in les on physical properties of final 1971.
- led release matrix tablets: fluid bed rm 16:581-590, 1990.
87. SC Wan Lucy, PWS Heng, G Muhuri. Incorporation and distribution of a low dose drug in granules. Int J Pharm 88:159-163, 1992.
88. F Higashide, Y Miki, Y Nozawa, K Ishibashi. Dependence of drug content uniformity on particle sizes in fluidized bed granulation. Pharm Ind 47:1202-1205, 1985.
89. WL Davies, WT Gloor Jr. Batch production of pharmaceutical granulation in fluidized bed II: effects of various binders and their concentrations on granulations and compressed tablets. J Pharm Sci 61:618, 1972.
90. WL Davies, WT Gloor Jr. Batch production of pharmaceutical granulation in fluidized bed III: binder dilution effects on granulation. J Pharm Sci 62:170, 1973.
91. FA Rawley. Effects of the bag shaking cycle on the particle size distribution of granulation. Pharm Technol 13(9):78-82, 1989.
92. JA Bonck. Spray granulation. Presented at the AIChE Annual Meeting, November 1993.
93. AAPS/FDA. Scale-up of oral solid dosage forms, December 11-13, 1991.
94. FDA. Immediate release solid dosage forms, scale-up and post approval changes: chemistry, manufacturing and control, in-vitro dissolution testing and in-vivo bioequivalence documentation. Rockville, MD: FDA Center for Drug Evaluation and Research, November 30, 1995.
95. DM Jones. Factors to consider in fluid bed processing. Pharm Technol 9(4):50, 1985.
96. EJ Simon. Fluid bed processing of bulk solids. Presented at the Third International Powder Technology and Bulk Solids Conference. February 20, PowTech Harrogate, UK: Heyden & Sons, 1975; 63-73.
97. W Kulling. Method and apparatus for removing a vaporized liquid from gas for use in a process based on the fluidized bed principle. US Patent 4,145,818, March 27, 1979.
98. DM Parikh. Fluid bed processing in the 1990s, 1996 Tableting and Granulation Year Book. Pharm Tech Suppl Oct:40-47, 1996.
99. International patent WO 95/20432, 1995.
100. VL Henkel, H Henning. On-line moisture measurement in fluid bed dryers. Pharm Ind 54:1047-1049, 1992.
101. US patent 5,392,531, 1991; European patent 0507038A1, 1991.
102. Japanese patent application, 61-259696, 1986.
103. Swiss patent 0176/93, 1993; US patent 5,444,892, 1995; European patent 0572356A1.
104. US patent, 3,671,296, June 20, 1977.
105. US patent, 4,034,126, July 5, 1977.
106. US patent, 4,542,043, Sept 17, 1985.
107. KF Jäger, KH Bauer. Effect of material motion on agglomeration in the rotary fluidized-bed granulator. Drugs Made Germ 25:61-65, 1982.
108. Türkoglu, Murat, He Min, Sakr Adel. Evaluation of rotary fluidized-bed as a wet granulation equipment. Eur J Pharm Biopharm 41:388-394, 1995.
109. Li Shun Por, CR Kowarski, KW Field, WM Grim. Recent advances in microencapsulation technology and equipment. Drug Dev Ind Pharm 14:353-376, 1988.

110. RL Robinson, G Hollenbeck. Manufacture of spherical acetaminophen pellets: comparison of rotary processing with multiple-step extrusion and spheronization. *Pharm Technol* 15(5):48–56, 1991.
111. DM Parikh. Layering in rotary fluid bed a unique process for the production of spherical pellets for controlled release. Presented at Interphex–USA, New York, May 18, 1991.
112. GA Hileman, RE Sarabia. Manufacture of immediate and controlled release spheres in a single unit using fluid bed rotor insert. Presented at the Annual Meeting of The American Association of Pharmaceutical Scientists (AAPS), Poster PT 6167, 1992.
113. RM Iyer, LL Augsburger, DM Parikh. Evaluation of drug layering and coating: effect of process mode and binder level. *Drug Dev Ind Pharm* 19:9891–998, 1993.
114. DM Parikh, et al. Unpublished data.
115. US patent, 5,132,142, 1992.
116. International patent WO 93/08923, 1993.
117. US patent 4,740,390.
118. FDA. Guide to inspection of validation of cleaning processes. July 1993.
119. DW Mendenhall. Cleaning validation. *Drug Dev Ind Pharm* 15:2105–2114, 1989.
120. SW Harder. The validation of cleaning procedures. *Pharm Technol* 8(5):29–34, 1984.
121. Validation of cleaning methods for processing equipment in pharmaceutical manufacturing. Association of the Swedish Pharmaceutical Industry, Stockholm, 1991.
122. GL Fourman, MV Mullen. Determining cleaning validation acceptance limits for pharmaceutical manufacturing operations. *Pharm Technol* 17(4):54–60, 1993.
123. AO Zeller. Cleaning validation and residue limits: a contribution to current discussions. *Pharm Technol* 17(10):70–80, 1993.
124. AH Tuthill. Stainless steel: surface cleanliness. *Pharm Eng* 14(6):34–44, 1994.
125. MK Doelling, et al. The development of a microwave fluid bed processor I: construction and qualification of a prototype laboratory unit. *Pharm Res* 9:1487–1492, 1992.
126. MK Doelling, RA Nash. The development of a microwave fluid bed processor II: drying performance and physical characteristics of typical pharmaceutical granulations. *Pharm Res* 9:1493–1501, 1992.
127. B Luy, P Hirschfeld, H Leuenberger. Granulation and drying in vacuum fluid-bed system. *Pharm Ind* 51:89, 1989.

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of spherical acetaminophen pellets:  
multiple-step extrusion and spheroni-

unique process for the production  
Presented at Interphex-USA, New

f immediate and controlled release  
tor insert. Presented at the Annual  
Pharmaceutical Scientists (AAPS),

valuation of drug layering and coat-  
el. Drug Dev Ind Pharm 19:9891-

cleaning processes. July 1993.  
g Dev Ind Pharm 15:2105-2114,

cedures. Pharm Technol 8(5):29-

ssing equipment in pharmaceutical  
h Pharmaceutical Industry, Stock-

eaning validation acceptance limits  
ons. Pharm Technol 17(4):54-60,

he limits: a contribution to current  
, 1993.

hliness. Pharm Eng 14(6):34-44,

a microwave fluid bed processor I:  
ype laboratory unit. Pharm Res 9:

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## Single-Pot Processing

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## I. INTRODUCTION

Single-pot processing was developed to provide the means for mixing, granulating, drying, and blending pharmaceutical granulations in a single apparatus. Although equipment design varies from manufacturer to manufacturer (Figs. 1–4), this category of processors is comprised of a high or low shear mixer–granulator (similar to conventional granulators) and outfitted with a variety of drying options. Initially, vacuum was combined with a heat-jacketed bowl to provide the means for drying in the single pot. Today, processors are available that provide vacuum drying with microwaves or that percolate gas under low pressure into the vacuum chamber (i.e., processing bowl).

Single-pot processors for the pharmaceutical industry have been available for years. They received renewed interest in the mid-1980s when microwaves were coupled with vacuum to enhance the drying operation. Microwaves applied to drying pharmaceutical granulations became synonymous with single-pot processing, and there was an anticipation that this technology would eventually become the norm for granulation processing. Several major pharmaceutical companies purchased production-scale units following successful trials conducted at vendors' pilot facilities. In the ensuing years, when the technology did not become as popular as expected, there were rumors that microwave systems could not be validated and suffered from excessive regulatory hurdles. The reality is neither, and single-pot technology has continued to evolve during the last decade. It has deemphasized its association with microwave drying while continuing to demonstrate its appropriate role in granulation technology [1].

In a production setting, single-pot processing may offer a number of advantages. By integrating granulating and drying capabilities into a single unit, capital investment in equipment and good manufacturing practice (GMP) floor space may be lower than other alternatives. The number of material-handling steps are decreased; consequently, the total processing time may be shorter while maintaining a high yield and keeping production support to a minimum. Environmental variables, such as humidity, are eliminated from the manufacturing process, which may offer advantages for processing moisture-sensitive formulations. Most single-pot processors may

## Single-Pot Processing



**Fig. 1** Niro Spectrum SP.1200 of Niro Inc., Aeromatic-Fielder

be outfitted with wash-in-place by minimizing exposure to the lining. Requirements for solvent processors compared with the dryers. Single-pot processors are processing events that are explosive exposure limits.

The versatility and compactness of single-pot processors also make them ideal for laboratory facilities (Fig. 5). Manufacturers began offering single-

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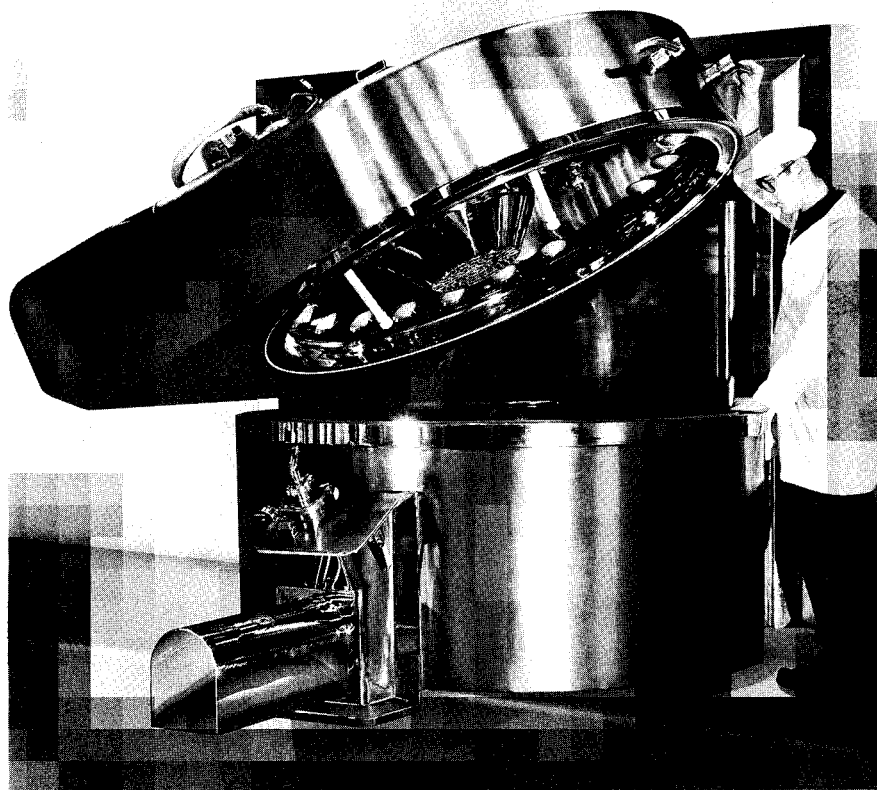
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provide the means for mixing, granulation, and drying in a single apparatus. From manufacturer to manufacturer, the equipment is comprised of a high or low shear granulator (or granulators) and outfitted with vacuum. Vacuum was combined with a heat source for drying in the single pot. Today, vacuum drying with microwaves or in the vacuum chamber (i.e., pro-

cessing in the pharmaceutical industry have been available. Interest in the mid-1980s when the technology to enhance the drying operation. Pharmaceutical granulations became synonymous with vacuum. There was an anticipation that this would become a norm for granulation processing. Manufacturers purchased production-scale units for their vendors' pilot facilities. In the end, it did not become as popular as expected, as the technology could not be validated and sufficient. The reality is neither, and single-pot processing has been drying the last decade. It has deemed vacuum drying while continuing to advance granulation technology [1].

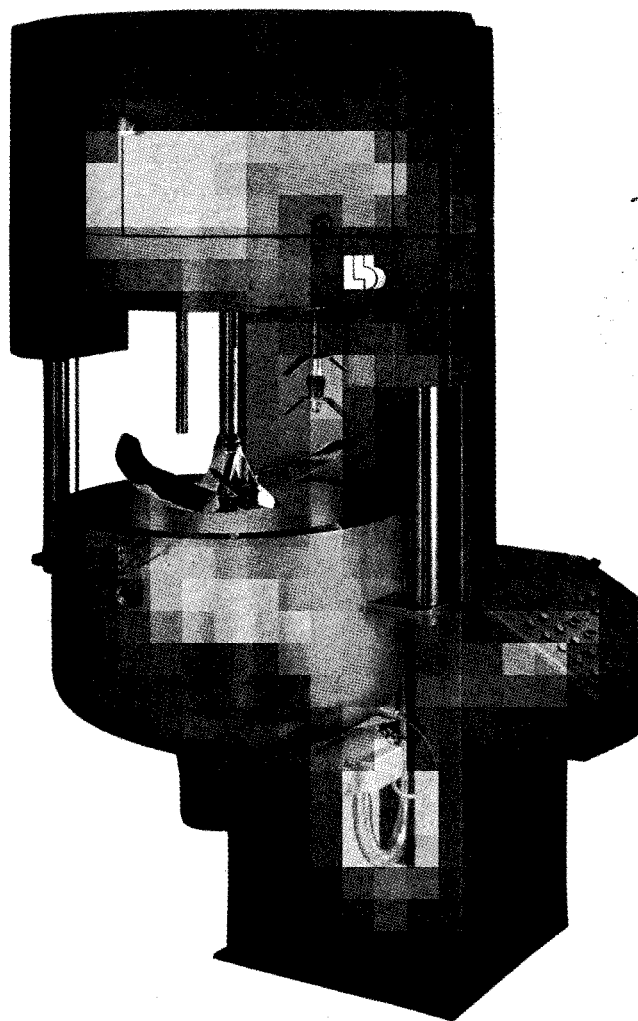
Single-pot processing may offer a number of advantages and drying capabilities into a single unit. It is a good manufacturing practice and offers other alternatives. The number of units required, consequently, the total processing time, high yield and keeping production costs low. Variables, such as humidity, are eliminated, which may offer advantages for manufacturers. Most single-pot processors may



**Fig. 1** Niro Spectrum SP.1200 microwave/vacuum single-pot processor. (Courtesy of Niro Inc., Aeromatic-Fielder Division, Columbia MD.)

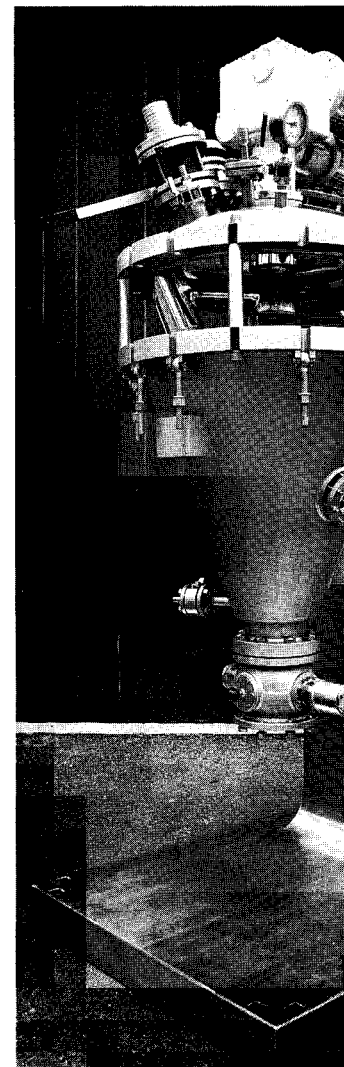
be outfitted with wash-in-place systems, thereby enhancing operator safety by minimizing exposure to the product both during manufacturing and cleaning. Requirements for solvent recovery systems are lower for single-pot processors compared with the high-volume scrubbers needed for fluid bed dryers. Single-pot processors outfitted with vacuum are attractive for evaporating events that are explosive or for containing drug substances with low-exposure limits.

The versatility and compactness of small-scale (3- to 25-L) single-pot processors also make the technology attractive for development and pilot laboratory facilities (Fig. 5). Within the last few years, equipment manufacturers began offering single-pot processors that can accommodate the batch

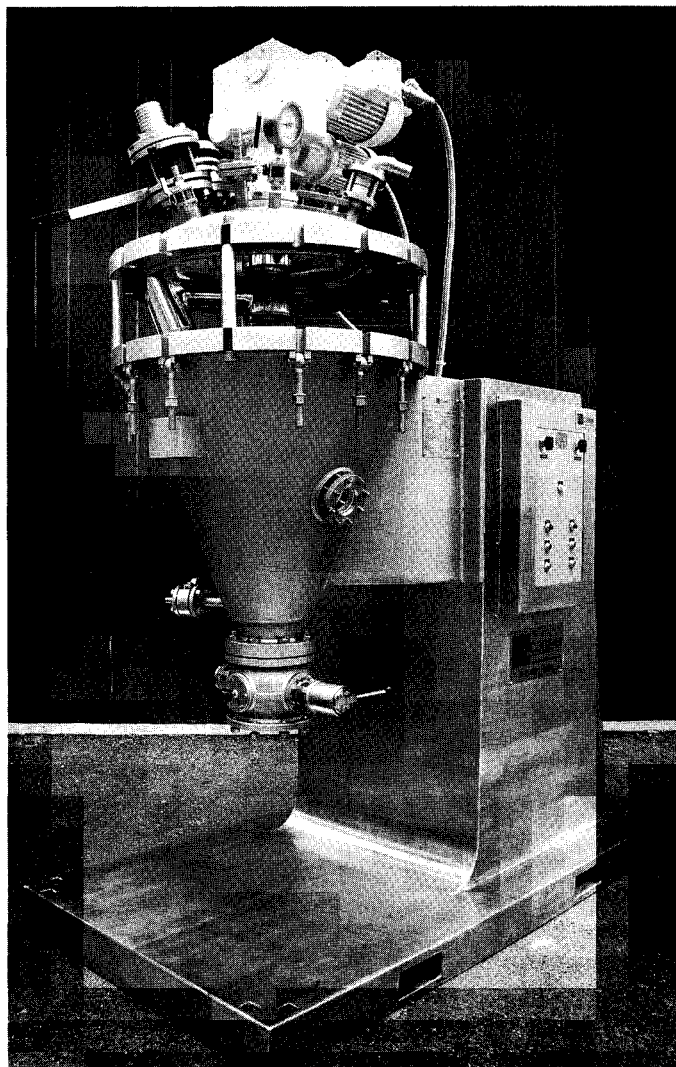


**Fig. 2** L. B. Bohle GMA 300 vacuum single-pot processor. (Courtesy of L. B. Bohle, Bristol PA.)

sizes required during early development (0.3 g–10 kg). The processors can be used as mixer–blenders for direct compression formulations, or as mixer–granulators to prepare wet granulations for fluid bed drying, or utilized for their full range of capabilities as a single-processing unit for all the steps required for granulation preparation. Some vendors offer the option of upgrading their small-scale processors. For example, a user can initially



**Fig. 3** 3V Cogeim Mixodry M Inc., Cogeim Equipment Division

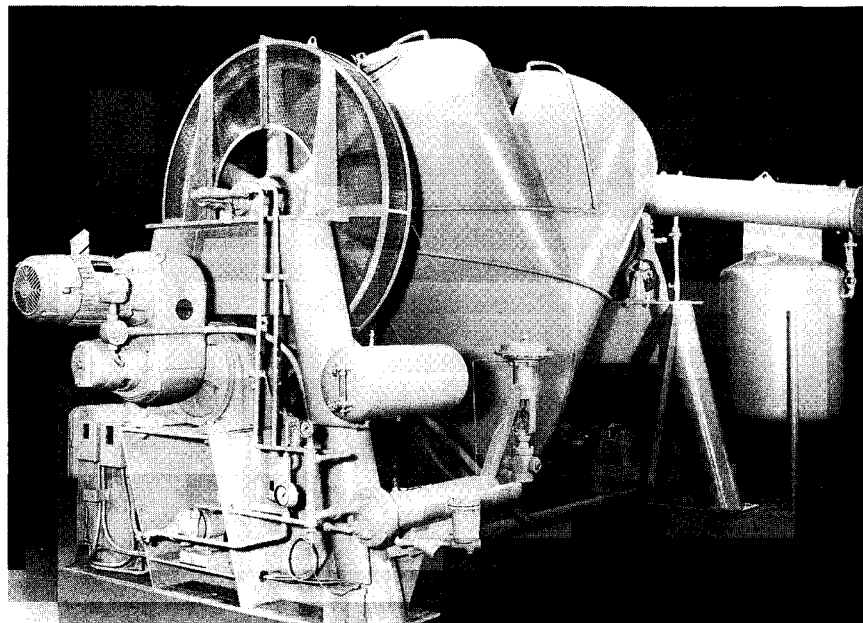


**Fig. 3** 3V Cogeim Mixodry Model EV vacuum solids processor. (Courtesy of 3V Inc., Cogeim Equipment Division, Charlotte NC.)

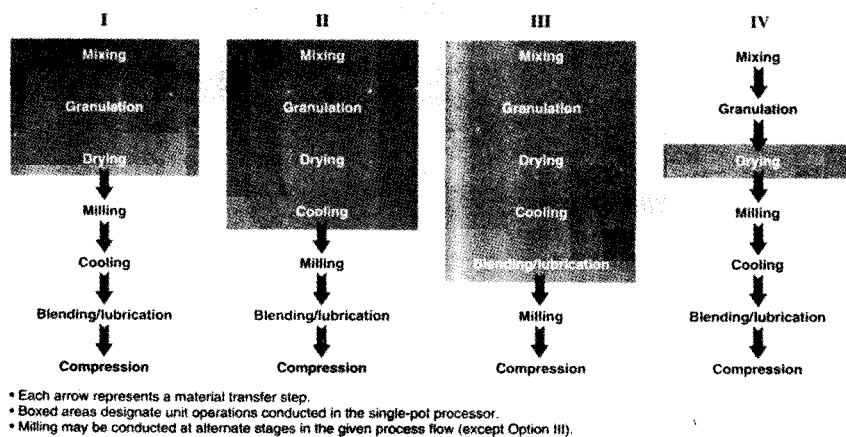
e-pot processor. (Courtesy of L. B.

0.3 g–10 kg). The processors can  
compression formulations, or as  
ions for fluid bed drying, or util-  
single-processing unit for all the  
Some vendors offer the option of  
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**Fig. 4** Patterson-Kelley 100 ft<sup>3</sup> twin shell solids processor. (Courtesy of Patterson-Kelley Co., East Stroudsburg PA.)



**Fig. 5** Options for using single-pot processor.

## Single-Pot Processing

purchase a single-pot processor. A microwave-drying system and a vacuum pump should be given strong consideration in a laboratory or pilot plant installation. The pharmaceutical formulation engineer should be aware of the capabilities and limitations of the single-pot processor.

The following text is intended to provide a general overview of the methods, the capabilities, and the limitations of the single-pot processor for pharmaceutical granulations. Flow diagrams depicting the mix, granulate, and dry granulation process are included in this chapter because it is a common process.

## II. TYPICAL SINGLE-POT PROCESSING

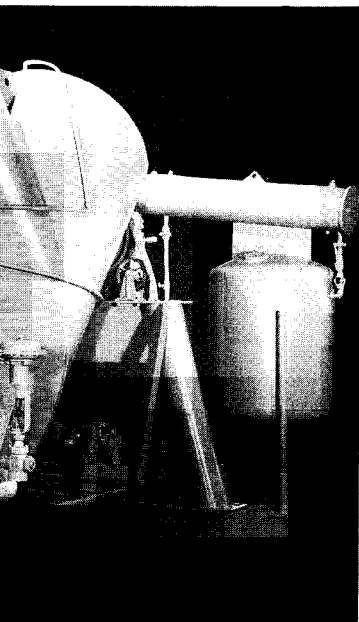
The steps and sequence of operations for single-pot processing are the same as for the multi-pot process, except that several of the steps are combined. The majority of production units have the capability to mix and dry granulations during the same process. A flow diagram depicting the single-pot granulation process is shown in Figure 5.

### A. Dry Mixing

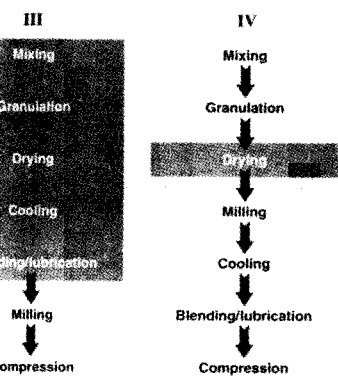
Powders are loaded into the processor (in a laboratory and pilot-scale units) or by a vacuum pump(s) used for the processor. Pneumatic- and mechanical mixing operators minimize operator exposure to the dry state until the desired granulation is achieved. The geometry of the processor, the blades, optimal mixing for granulation, and the time charged to 50–75% of capacity are variables that affect the addition of the binder solution.

### B. Addition of Binder Solution

Once dry mixing is complete, the binder solution is added (connected to a solvent reservoir and a peristaltic pump). Because the binder solution is added at this point, all variables affecting the granulation process are controlled.



ds processor. (Courtesy of Patterson-



Option III).

purchase a single-pot processor with vacuum-drying capabilities and add a microwave-drying system at a later time. Consequently, single-pot processors should be given strong consideration when equipping a development laboratory or pilot plant intended to offer a variety of processing options to the pharmaceutical formulator.

The following text is intended to expose the reader to the drying methods, the capabilities, and the applications of single-pot processing to pharmaceutical granulations. Fluid bed technology, which can also be used to mix, granulate, and dry granulation in a single unit, will not be addressed in this chapter because it is discussed elsewhere in this book.

## II. TYPICAL SINGLE-POT PROCESS

The steps and sequence of manufacturing pharmaceutical granulations using single-pot processing are the same as those that use alternative technologies, except that several of the steps are performed in the same product chamber. The majority of production installations make use of its mixing, granulating, and drying capabilities during the processing of a single batch. Figure 6 is a flow diagram depicting each unit operation involved in a typical single-pot granulation process.

### A. Dry Mixing

Powders are loaded into the single pot either manually (for development- and pilot-scale units) or by a conveying system (for production-scale units). Vacuum pump(s) used for the drying operation can also be used to charge the processor. Pneumatic- and vacuum-conveying systems contribute to minimizing operator exposure to the drug product. The powders are mixed in the dry state until the desired degree of uniformity is obtained. Depending on the geometry of the processing bowl and the efficiency of its mixing blades, optimal mixing for most processors generally occurs when the bowl is charged to 50–75% of capacity. Batch size, impeller speed, and mixing time are variables that affect the desired degree of blend homogeneity before the addition of the binder solution.

### B. Addition of Binder Solution

Once dry mixing is completed, the binder solution is added through a spray lance connected to a solvent delivery system (such as a pressure pot or peristaltic pump). Because the single-pot processor is operating as a granulator at this point, all variables considered during the manufacture of wet

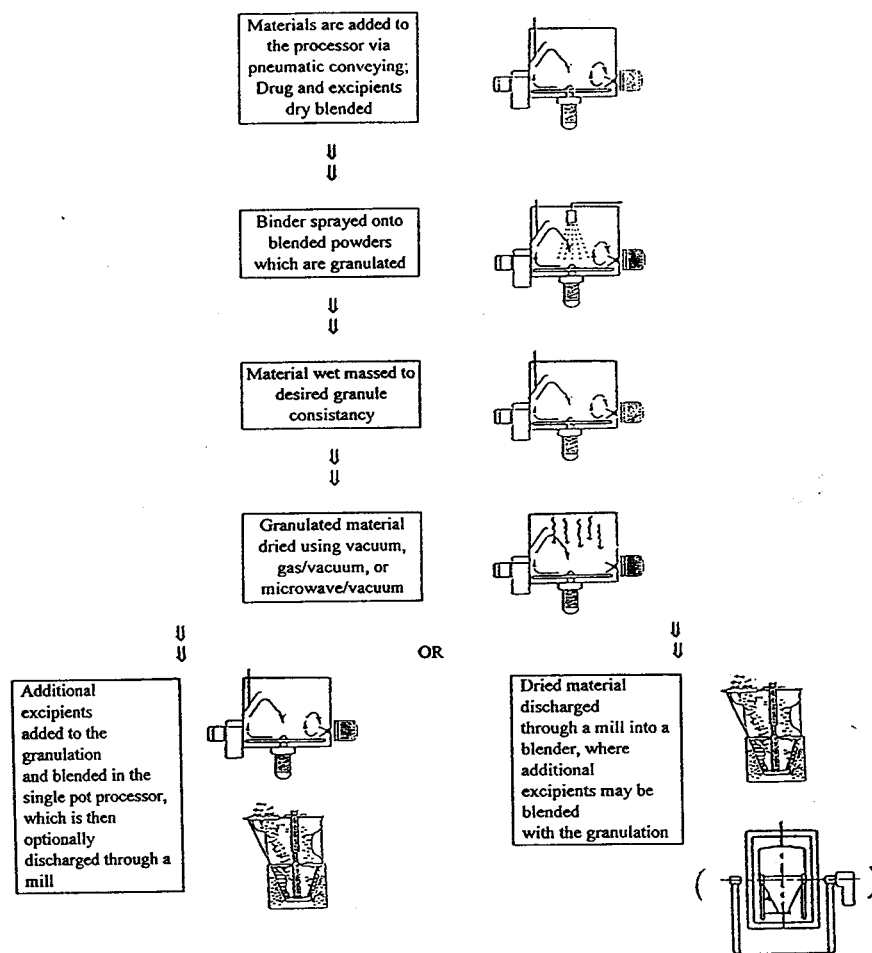


Fig. 6 Typical process flow diagram for single-pot process.

granulations in conventional high or low shear mixer-granulators are applicable. Those variables include the rate of binder action, droplet size, and spray pattern (the latter two being determined by the selection of the spray nozzle and the distance between the nozzle tip and granulation bed). The speed of the main impeller and the granulating tool (e.g., high-intensity chopper bar), as well as the jacket temperature, should also be controlled during binder addition.

### C. Wet Massing

Following binder addition, granulation until the desired consistency is reached. The design variables that can affect the granulation process. Granulation endpoint may be determined by the product bed, and the energy

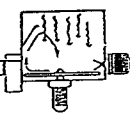
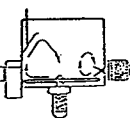
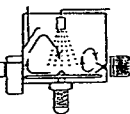
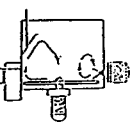
### D. Drying

After granulation, the material is dried. (a) vacuum drying; (b) gas-assisted drying. Details of each drying process. The product bed is usually stirred to facilitate solvent removal and to prevent caking of the granulation or by slowly rotating the bowl continuously or intermittently to avoid granule degradation. Variables exercised to avoid granule degradation include the level of vacuum and the degree of agitation. During drying, gas-assisted vacuum drying, gas used and its rate of delivery are all of the variables used for drying. level of microwave power is also a variable.

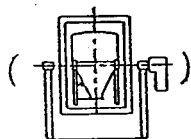
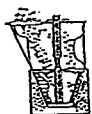
If required, cooling operation. The heated water jacket or conductive heat during the drying process. A water solution to provide a cooling effect to cool the granulation is by agitating the granulation bed.

### E. Sizing and Lubrication

Once the granulation is dried, it is accomplished by discharging the granulation into a receiving vessel where it may be lubricated and flavors. This is the final step of the single-pot process.



Dried material discharged through a mill into a blender, where additional excipients may be blended with the granulation



single-pot process.

shear mixer-granulators are ap-  
of binder action, droplet size, and  
ned by the selection of the spray  
e tip and granulation bed). The  
ulating tool (e.g., high-intensity  
ature, should also be controlled

### C. Wet Massing

Following binder addition, additional energy may be imparted to the granulation until the desired consistency is obtained. The speeds of the main impeller and granulating tool, wet-massing time, and jacket temperature are variables that can affect the physical attributes of the granulation. Impeller design will also affect the amount of shear imparted to the granulation. Granulation endpoint may be controlled by process time, temperature of the product bed, and the energy consumption or torque of the main impeller.

### D. Drying

After granulation, the material is dried using one of three approaches: (a) vacuum drying; (b) gas-assisted vacuum drying; or (c) microwave-vacuum drying. Details of each drying method are summarized in Section III. The product bed is usually stirred at low intensity during the drying process to facilitate solvent removal and promote uniform drying, as well as to prevent caking of the granulation on the chamber's walls. Agitation may be applied by slowly rotating the bowl or operating the impeller at low speed either continuously or intermittently throughout the drying stage. Caution must be exercised to avoid granule breakdown during drying, which may result in unfavorable compression characteristics [2]. Variables for vacuum drying include the level of vacuum maintained in the bowl, the jacket temperature, and the degree of agitation. In addition to the parameters listed for vacuum drying, gas-assisted vacuum drying must also consider the type of drying gas used and its rate of delivery. When microwave-vacuum drying is used, all of the variables used for vacuum drying are applicable, as well as the level of microwave power used to dry the granulation.

If required, cooling can be conducted at the conclusion of the drying operation. The heated water or steam in the bowl jacket, which supplied conductive heat during the drying process, can be replaced with a glycol-water solution to provide a contact surface as low as 10°C. Another approach to cool the granulation is by purging a cooling gas into the single pot while agitating the granulation bed.

### E. Sizing and Lubrication

Once the granulation is dried, it is usually necessary to size it. This may be accomplished by discharging the material through an in-line mill into a receiving vessel where it may be blended with any remaining excipients (e.g., lubricant and flavors). This process design maintains the containment benefits of the single-pot process. Alternatively, the remaining excipients may



ended with the granulation before requires that the lubricant be adequately transferred during the compression.

## POT PROCESSORS

Generally jacketed for temperature control, the granulating solvent and assists in the result, conductive heating provided by the single pot contributes to the transfer of heat through pharmaceutical granulation, prevents its use as the sole heating medium. Equation 1 addresses the conductive

the granulation bed is governed

(1)

ted wall  
between the contact wall and the

either by increasing the contact area of the bowl walls (which can be achieved by increasing the bowl), or by maximizing the contact area between the walls and product (either through increasing the temperature of the product or by increasing the temperature of the product).

may be of some value for the design of the heating [3]:

(2)

$V$  = vessel working volume ( $\text{m}^3$ )

$a$  = refers to pilot-scale

$b$  = refers to production-scale

This relation accounts for the ratio of the surface area of the jacketed bowl and the volume of the product requiring drying.

## B. Vacuum Drying

Single-pot processors using vacuum drying may be considered if the product must be dried at low temperature ( $< 40^\circ\text{C}$ ), if solvent recovery is required, or if the potential for explosion is high. A vacuum is maintained within the vessel, thereby lowering the temperature at which the granulating solvent evaporates. Because vapors are removed from the processing bowl, vacuum drying provides a convenient means for solvent recovery.

De Smet [4] has discussed the theory, advantages, and limitations of vacuum drying. Aqueous granulations require a large amount of energy during drying, which is generally supplied by the transfer of heat through conduction from the jacketed bowl to the product. The amount of energy required for water removal is dependent on the level of vacuum applied to the vessel and the osmotic pressure of dissolved substances. As additional material dissolves in the water, the osmotic pressure increases and additional energy is necessary to drive off the water. Therefore, as the material becomes drier, the amount of energy necessary to evaporate the water increases, and the rate of evaporation slows. Processing times in vacuum dryers are often long, owing to the limited contact of the granulation with the heat from the jacketed walls, and the slow rate of evaporation of the solvent from the interior of the granules.

The drying rate of the vacuum component is dependent on the following relation:

$$V = ks\Delta P \quad (3)$$

where:

$V$  = evaporation rate

$k$  = rate coefficient

$s$  = total surface of granules

$\Delta P$  = the vapor pressure difference between the granules and the surrounding space

The rate of drying can be facilitated by increasing the level of vacuum (i.e., decreasing the pressure within the bowl) to increase the differential between granule and bowl vapor pressure. Figure 7 is a typical drying curve

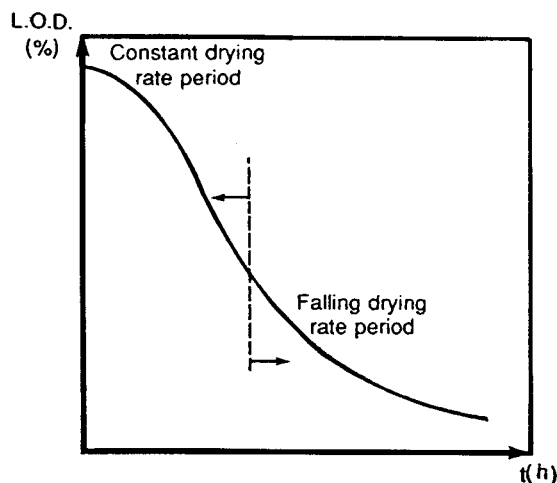


Fig. 7 Typical curve for vacuum drying. (Courtesy of Manufacturing Chemist.)

for a vacuum-drying process. When moisture content in the granulation is high, the rate of drying is constant because evaporation of solvent from the product surface readily occurs. As the level of moisture on the granule surface decreases, water must migrate from the interior of the granule before evaporation. As a result, the rate of evaporation progressively decreases.

During vacuum-drying processes, one should be aware of various problems that could arise. For example, granule damage may occur owing to excessive attrition as the bed is agitated during drying. Vacuum systems should contain adequate filtering or blowback to prevent the loss of granulation "fines" through the vacuum line, which may compromise the drug uniformity within the processed batch.

A condenser positioned between the processor and vacuum pump, should always be used, especially for granulations manufactured using organic solvents. The condensate must be sufficiently cooled to prevent it from being released into the atmosphere. Also, filters may become blocked owing to condensation forming on the filter or the entrapment of solid particles. Blockage of the filters reduces the level of vacuum that can be pulled on the bowl and excessively strains the pump itself.

### C. Gas-Assisted Vacuum Drying

Accelerating the drying process in vacuum dryers is often limited by characteristics of the product or equipment. Bowl temperature is generally lim-

ited by the physicochemical properties of higher temperatures to control the balance between the product and the equipment. The design of the equipment must consider considerable granule attrition and the compression properties.

Gas-assisted vacuum dryers are processors that use vacuum drying with the addition of gas through the granulation. Drying can be performed at lower temperatures (longer drying), but at shorter-process times.

The gas may be introduced from the bottom of the vessel or through the top. Nitrogen (mixed with or without oxygen), units. The rate of gas flow must be adjusted for a specific product.

The introduction of gas into the process through several actions can improve the transport of the product. A solvent recovery system [which uses the vapor pressure driving force] is increased, resulting in a faster drying time by increasing the differential between the granule and the drying time by increasing the bed. In addition to improving the drying time, it can reduce or eliminate product loss because it improves flow and

### D. Microwave-Vacuum Drying

High shear granulators with vacuum drying are the fastest drying rates in the industry. Drying is based on the absorption of microwave materials, the theory of which is that microwave waves are a form of electromagnetic radiation (frequencies of which fall between radio waves and optical waves). The two frequencies used for industrial purposes are 2450 MHz and 915 MHz. Processors generally use 2450 MHz when used in conjunction

ited by the physicochemical stability of the product, which can limit the use of higher temperatures to expedite drying. Increasing the contact area between the product and the vessel is difficult without significantly altering the design of the equipment. Excessive agitation of the product can lead to considerable granule attrition, which can lead to poor granulation flow and compression properties.

Gas-assisted vacuum drying improves the efficiency of single-pot processors that use vacuum drying by continuously introducing a small stream of gas through the granulation to facilitate solvent removal. Drying continues to be performed at lower temperatures (compared with tray and fluid bed drying), but at shorter-processing times than vacuum drying alone.

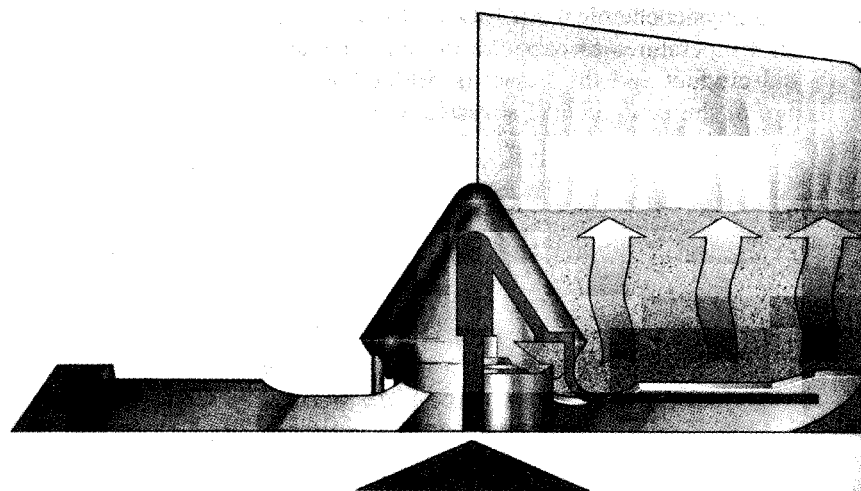
The gas may be introduced into the unit through openings in the bottom of the vessel or through the mixing blades (Fig. 8). Compressed air or nitrogen (mixed with or without air) are commonly used gases for these units. The rate of gas flow and the level of vacuum applied to the bowl can be adjusted for a specific product to produce optimal drying conditions.

The introduction of gas into a vacuum chamber facilitates the drying process through several actions. The constant flow of gas through the product improves the transport of moisture from the product to the vacuum-solvent recovery system [5]. Introducing gas into the bowl also increases the vapor pressure driving force [6]. The pressure gradient across the vessel is increased, resulting in a reduction in the rate at which water molecules recombine, producing a net increase in the rate of evaporation. This causes the product temperature to be reduced, which increases the temperature differential between the granules and the bowl wall. The gas also reduces drying time by increasing the heat transfer coefficient from the bowl to the bed. In addition to improving the heat transport through the bed, the gas can reduce or eliminate product sticking to the sides of the vessel walls because it improves flow and dries the particle surfaces more quickly.

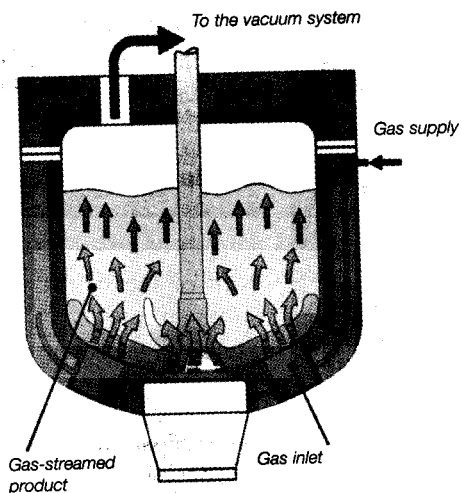
#### D. Microwave-Vacuum Drying

High shear granulators with microwave-vacuum-drying capabilities provide the fastest drying rates in the family of single-pot processors. Microwave drying is based on the absorption of electromagnetic radiation by dielectric materials, the theory of which has been extensively described [7-9]. Microwaves are a form of electromagnetic energy similar to radiowaves, the frequencies of which fall between 300 and 3000 MHz (between radio and optical waves). The two frequencies allocated for domestic, scientific, medical, and industrial purposes are 915 and 2450 MHz. Pharmaceutical processors generally use 2450 MHz, because this frequency is more desirable when used in conjunction with vacuum. Single-pot processors incorporating





(a)



(b)

**Fig. 8** Gas introduction and flow-through vacuum/gas dryers: (a) through blades; (b) through bottom of bowl. (a) Courtesy of Niro Inc., Aeromatic-Fielder Division, Columbia MD; (b) Courtesy of L. B. Bohle, Bristol PA.

microwave drying are constant. The common reflector of microwave processing chamber. Teflon is a suitable material for components and temperature problems.

Energy absorption of material is given by Eq. (4) [8,9]:

$$P = 2\pi f V^2 E_0 E_r \tan \delta$$

where:

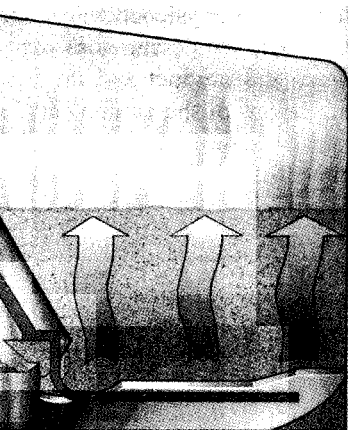
- $P$  = the power density
- $f$  = frequency (Hz)
- $V$  = voltage gradient
- $E_0$  = dielectric permittivity
- $E_r$  = dielectric constant
- $\tan \delta$  = loss tangent

For a constant electric field, the power absorbed is proportional to the loss factor, which is a measure of the microwave energy.

Various materials commonly used in pharmaceutical granulation have low loss factors and only a few solvents used in the granulation process (such as water, methanol, etc.), however, possess high loss factors [8]. The dipolar components of the material absorb the frequency electromagnetic field, resulting in its evaporation from the chamber. Table 1 lists the loss factors for typical pharmaceutical granulation.

**Table 1** Loss Factors for Common Pharmaceutical Granulation

Ingredient	Percent (w/w)
Water	22
Binder-disintegrant	24
Flow enhancer	2
Drug substance	52



microwave drying are constructed of stainless steel because metal is a common reflector of microwave energy and contains the energy within the processing chamber. Teflon is essentially inert to microwaves, making it a suitable material for components required in the processing bowl (e.g., spray lance and temperature probe).

Energy absorption of materials exposed to microwaves is described by Eq. (4) [8,9]:

$$P = 2\pi f V^2 E_0 E_r \tan \delta \quad (4)$$

where:

$P$  = the power density of the material ( $\text{W/m}^3$ )

$f$  = frequency (Hz)

$V$  = voltage gradient ( $\text{V/m}$ )

$E_0$  = dielectric permmissivity of free space ( $8.85 \times 10^{-12} \text{ F/m}$ )

$E_r$  = dielectric constant of the material

$\tan \delta$  = loss tangent

For a constant electric field strength  $V$  the term  $[2\pi f V^2 E_0]$  is constant. Therefore, the power absorbed is proportional to the term  $[E_r \tan \delta]$ , called the loss factor, which is a relative measure of how easily a material absorbs microwave energy.

Various materials commonly used in pharmaceutical formulations have low loss factors and only absorb microwave energy at high field strengths. Solvents used in the granulation process (water, ethanol, isopropanol, and such), however, possess high loss factors relative to the pharmaceutical powders [8]. The dipolar component of the solvents couples with the high-frequency electromagnetic field producing high heating rates for the solvent, resulting in its evaporation and subsequent removal from the processing chamber. Table 1 lists the loss factors for various components in a typical pharmaceutical granulation [10].

**Table 1** Loss Factors for Components in Typical Pharmaceutical Granulation

Ingredient	Percent (w/w)	Loss factor
Water	22	6.1
Binder-disintegrant	24	0.41
Flow enhancer	2	0.001
Drug substance	52	0.001

uum/gas dryers: (a) through blades;  
ro Inc., Aeromatic-Fielder Division,  
istol PA.

Magnetrons are the source of microwave energy and may be either fixed or variable in their manner of introducing microwaves into the product bowl. Fixed-output magnetrons regulate the forward power into the processing bowl by cycling on and off (duty cycling). Consequently, at any particular time, the forward power is either at its maximum or at zero. Variable-power magnetrons control power directly by adjusting wattage. Magnetrons are either water- or air-cooled to dissipate generated heat. Because water has a greater heat capacity, it is a more efficient medium than air to cool the magnetrons.

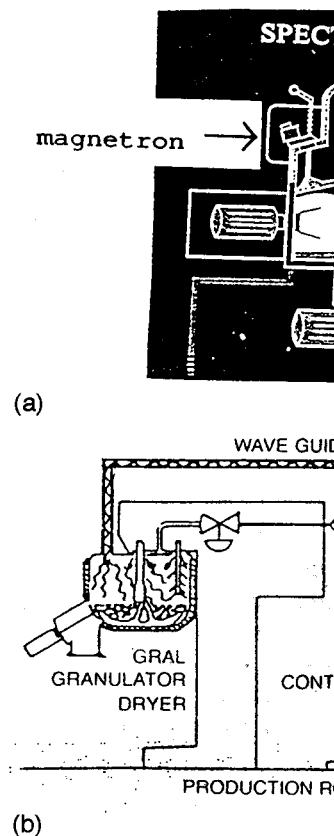
Fixed-output magnetrons are positioned in the lid or around the periphery of the processing bowl, whereas variable-output magnetrons are housed in a separate room (Fig. 9). Positioning the magnetrons in a separate area (such as a service chase) provides easier access for servicing, but requires the use of waveguides that are several feet in length. (Waveguides are used to direct the microwave energy from the magnetron to the processing bowl.) Magnetrons located in the lid or the periphery of the bowl use short waveguides (15.2–30.5 cm; 6–12 in.) that do not require calibration (or tuning) to minimize microwave energy reflected back into the magnetron (reflected power). Nevertheless, when properly tuned, longer waveguides do not cause any additional difficulties.

E-field is a measure of the free or unabsorbed microwave energy and is detected by measuring the electrical component of the electromagnetic wave. Once a particular E-field level is reached, the forward power introduced into the processing bowl must be reduced. With fixed output magnetrons, this is done by increasing the duty cycling interval, while the wattage is reduced with variable-output magnetrons.

Lucisano and Moss [11] performed a study in which a microwave-drying process was conducted in two different processors, one using fixed-output magnetrons and the other using a variable power magnetron. The unit using fixed-output magnetrons had difficulty obtaining low moisture levels (< 0.3%) because the E-field safety setpoint was exceeded when the moisture went below 1%. This problem did not occur for the unit using the variable-power magnetron because forward power was reduced as the E-field increased. During the late stages of drying, the unit was primarily functioning as a vacuum dryer, as the amount of microwave energy being introduced into the bowl was minimal.

The use of vacuum during microwave drying lowers the temperature at which the solvent volatilizes, thereby limiting the temperature to which the material is exposed. For example, at a vacuum of 45 mbar, water-based granulations will dry at approximately 31°C. Once most of the water is removed from the process, the temperature of the material will rise as components in the mixture with lower loss factors start to absorb the micro-

## Single-Pot Processing



**Fig. 9** Magnetron location in two different microwave processing systems. Features include fixed output magnetrons located directly above product cavity, as in (a). Processor. Features include variable-output magnetron in a separate room, as in (b). Processor. Niro Inc., Aeromatic-Fielder Division.

waves. If too much vacuum is applied, granule breakdown owing to the low surface of the granules. Microwaves at 40–100 mbar. Introducing microwaves risks ignition of the surrounding material.

Control of the drying process involves measurement of product temperature

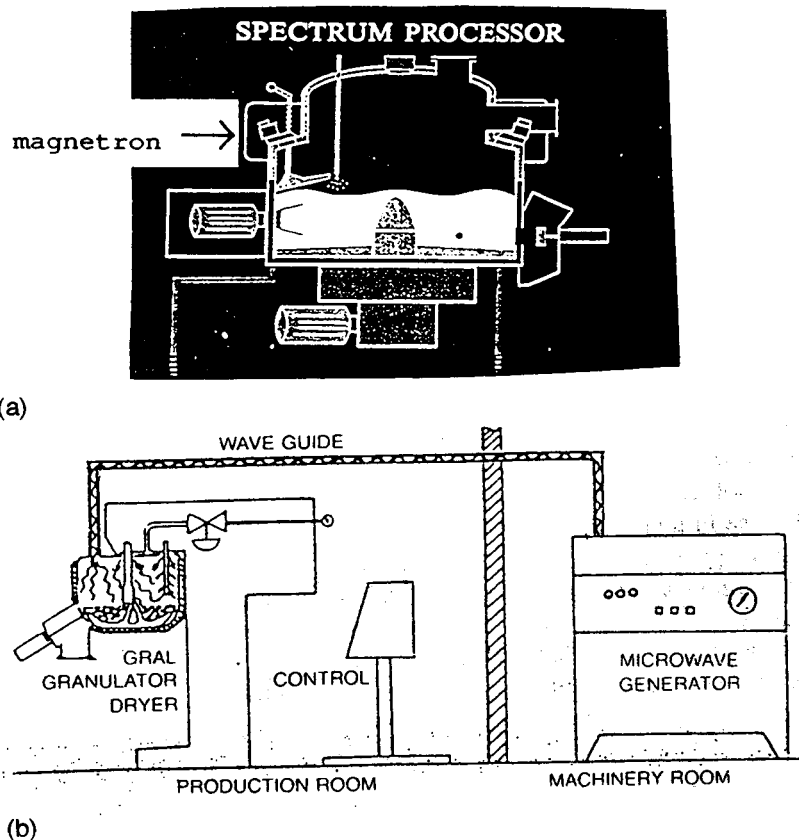
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**Fig. 9** Magnetron location in microwave processors: (a) Spectrum MW Processor. Features include fixed output magnetron, magnetrons arranged around perimeter directly above product cavity, and short waveguides (6–12 in.). (b) Vactron MW Processor. Features include variable output magnetrons, magnetrons located in room separate from product bowl, and long waveguides (several feet). (a) Courtesy of Niro Inc., Aeromatic-Fielder Division, (b) Courtesy of GEI Processing.

waves. If too much vacuum is applied to the system, there is a potential for granule breakdown owing to the excessive pressure between the core and surface of the granules. Microwaves are typically applied in a vacuum range of 40–100 mbar. Introducing microwaves into a vacuum less than 40 mbar risks ignition of the surrounding air, a condition known as “arcing.”

Control of the drying process is achieved through the simultaneous measurement of product temperature and electric field strength [8,9]. Figure 10

depicts the level of microwave power, E-field, and product temperature at various times during the drying process. During the initial stage, the product temperature remains relatively constant as the free solvent is preferentially evaporated, and the electric field strength remains relatively low. The amount of vacuum applied to the bowl, and to a lesser extent, the bowl jacket temperature, will affect the actual product temperature observed. As drying progresses at a constant rate of forward power, the amount of absorbed energy decreases as the material dries, thereby increasing the amount of free energy. As the free energy increases, a corresponding increase in the E-field is also observed.

The rise in E-field is accompanied by an increase in product temperature, which is simultaneously monitored while the magnetron output power is reduced. This is necessary because the loss factors for some pharmaceutical components are so small that very low moisture can be achieved before the temperature rises. For such materials, the E-field can rise sharply once most of the solvent has evaporated, resulting in significant temperature gains.

The rise in temperature and E-field signifies that the end of the drying process is approaching. Several factors, such as the loss factors of the formulation components, microwave power, and the solvent retention properties of the solids, influence the point at which the previous relation will occur. For example, lactose has a low loss factor and shows a sharp rise in E-field, followed by a slow temperature rise. Conversely, starch has a high loss factor and demonstrates a fast temperature rise followed by a slow rise in E-field.

#### IV. PRODUCT STABILITY

The stability of pharmaceutical granulations dried by microwaves is comparable with that provided by alternative methods. Microwaves are nonionizing and do not possess the amount of energy required for the formation of free radicals or the liberation of bound water—conditions that foster product instability.

At least a dozen new and supplemental drug applications that include the use of microwave-vacuum drying of wet granulations have been approved by the Food and Drug Administration (FDA). We are unaware of any instance in which the FDA required additional stability or analytical testing beyond that normally required for other methods of manufacture. Mandal [12], Moss [13], and others [14,15] have also published or presented data showing the comparability of the physicochemical characteristics of granulation dried in microwave processors versus tray dryers and fluid bed dryers.

#### Single-Pot Processing

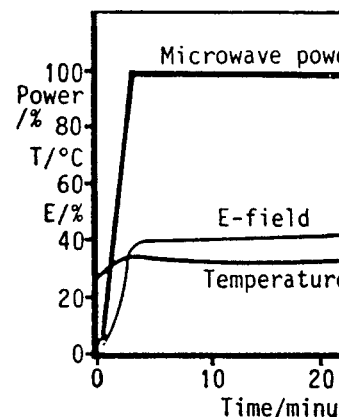


Fig. 10 Typical drying curve (courtesy of Manufacturing Chemist.)

Duschler and colleagues have shown that microwaves should not be generally recommended for drying pharmaceuticals after they enter the drying stage (due to the risk of thermal damage to active substances and to the variability of electric constants). The results of several installations of single-pot processing indicate that Duschler's findings indicate that Duschler's proper selection of formulation is critical.

#### V. SCALE-UP OF DRYING

Because the rate of solvent removal is a function of a favorable surface area/volume ratio, the rate often increases substantially as the scale-up is relatively insensitive to the surface area/volume ratio. The same inefficiency as vacuum drying is observed on a scale-up. Pearlsburg et al. have shown that the vacuum drying process for a 100 kg batch of granules to a drying endpoint of less than 30- to 45-min range through a 100 kg (Vactron.600), whereas the microwave drying process after additional scale-up to 500 kg is slightly to a 50- to 55-min range. The drying times when scaling-up

field, and product temperature at the initial stage, the product temperature is preferentially low. The amount of solvent removed remains relatively low. The amount of solvent removed, to a lesser extent, the bowl jacket temperature observed. As drying power increases, the amount of absorbed solvent increases. By increasing the amount of free solvent, there is a corresponding increase in the E-field.

By an increase in product temperature, while the magnetron output power remains constant, the loss factors for some pharmaceuticals can be achieved before the E-field can rise sharply once there is a significant temperature gain. This signifies that the end of the drying process, such as the loss factors of the formulation and the solvent retention properties, will occur. The previous relation will occur, and shows a sharp rise in E-field, and, conversely, starch has a high loss factor followed by a slow rise in E-field.

As dried by microwaves is common. Microwaves are nonionizing energy required for the formation of water—conditions that foster

al drug applications that include wet granulations have been applied (FDA). We are unaware of any additional stability or analytical data for other methods of manufacture. We have also published or presented data on the physicochemical characteristics of granules versus tray dryers and fluid bed

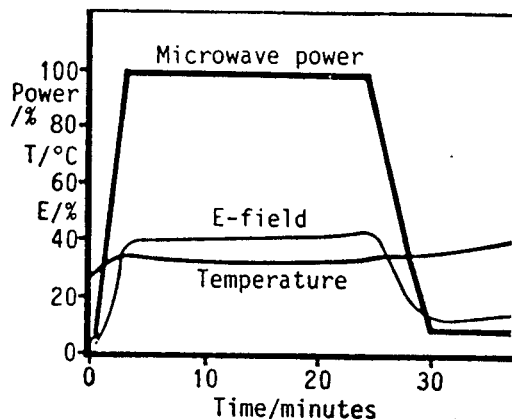


Fig. 10 Typical drying curve for microwave-vacuum drying. (Courtesy of Manufacturing Chemist.)

Duschler and colleagues [16] concluded that microwave drying could not be generally recommended because of the inability to control the microwaves after they enter the drying cavity and the risk of unacceptable thermal damage to active substances with high loss factors (i.e., high dielectric constants). The routine production of pharmaceutical products by several installations of single-pot processors using microwave-vacuum drying indicates that Duschler's general concerns can be addressed by the proper selection of formulation components and process parameters.

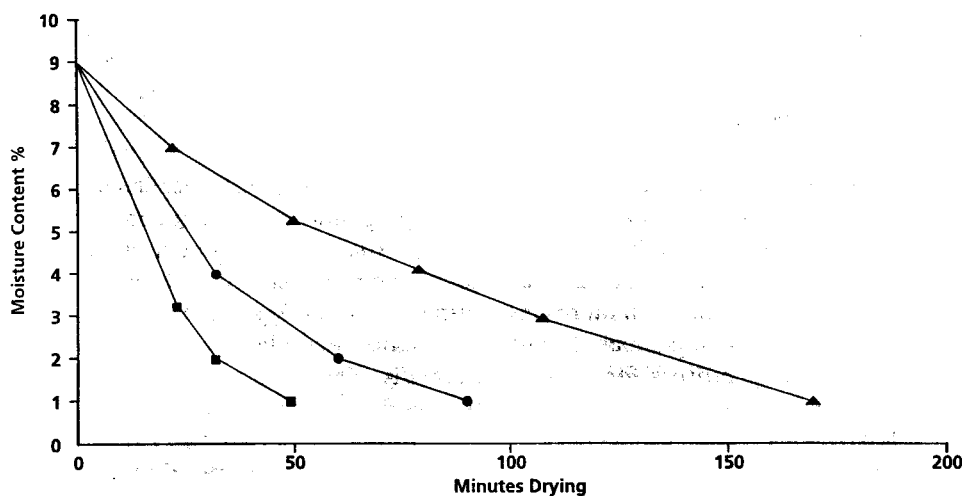
## V. SCALE-UP OF DRYING PROCESSES

Because the rate of solvent removal during vacuum drying is dependent on a favorable surface area/volume ratio, the drying time in a vacuum processor often increases substantially during scale-up. Microwave-vacuum drying is relatively insensitive to the surface area/volume ratio and does not suffer the same inefficiency as vacuum drying during transition from pilot- to production-scale. Pearlsweig et al. reported successfully scaling a microwave-vacuum drying process for a moisture-sensitive formulation that required a drying endpoint of less than 0.2% [17]. The drying time remained within a 30- to 45-min range throughout the scale-up from 15 kg (Vactron.75) to 300 kg (Vactron.600), whereas the time for vacuum drying increased threefold. After additional scale-up to 600 kg in a Vactron.1200, the drying time rose slightly to a 50- to 55-min range. Poska also reported attaining equivalent drying times when scaling-up in Spectrum processors ranging from 65- to

300-L-bowl size [14]. Figure 11 compares typical drying curves for a lactose–starch granulation prepared in single-pot processors using vacuum drying, gas-assisted vacuum drying, or microwave–vacuum drying. Although not as rapid as microwave–vacuum drying, gas-assisted vacuum drying can decrease the drying time by up to 50% compared with that of vacuum drying alone [5].

When performing feasibility trials on a development- or pilot-scale microwave–vacuum processor, it is important to be aware of the maximum power capacity of the corresponding, production-scale processor. For example, the maximum microwave power available to dry a 20-kg-batch size in the Vactron.75 is 0.25 kW/kg, whereas the Vactron.600 can provide only a maximum power of 0.12 kW/kg to dry a 200 kg batch. Table 2 compares the maximum power capacities for pilot-scale and production-scale units of three different brands of single-pot processors.

Figure 12 shows the similarity of drying curves for a 12% aqueous granulation between the Spectrum.65 and Vactron.75 when forward power and batch size were adjusted to assure the same power capacity. Figure 13 shows both the scalability of microwave–vacuum drying and the equivalent drying rates obtained in different processors for a 7% ethanol granulation when the microwave power and batch size are adjusted to assure consistency of power.

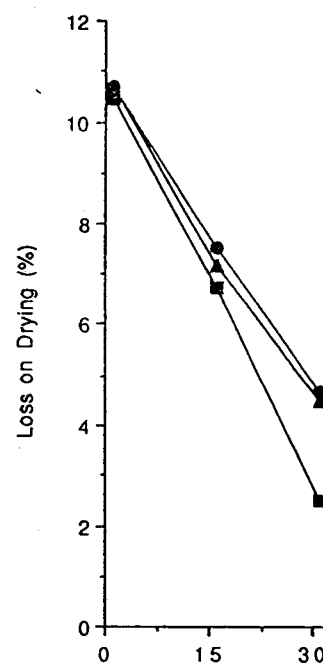


**Fig. 11** Comparison of drying curves for different modes of drying: ■, microwave; ●, vacuum with air; ▲, vacuum only. (Courtesy of Niro Inc., Columbia, MD.)

**Table 2** Maximum Power Capacity of Pilot-Scale and Production-Scale Microwave–Vacuum Single-Pot Processors

Pilot scale		Production scale
Processor	MMP <sup>a</sup>	
Vactron.75	0.25	Vactron.600
Vacumat.70	0.15	Vacumat.600
Spectrum.65	0.09	Spectrum.600

<sup>a</sup>MMP is the maximum microwave power available to dry a 20-kg-batch size at the pilot scale and the maximum power available to dry a 200-kg-batch size at the production scale.



**Fig. 12** Scalability of microwave–vacuum drying (12% aqueous granulation) for different processors. The drying rates were the same for all three processors.

typical drying curves for a single-pot processors using vacuum microwave-drying. All drying, gas-assisted vacuum drying, 100% compared with that of vac-

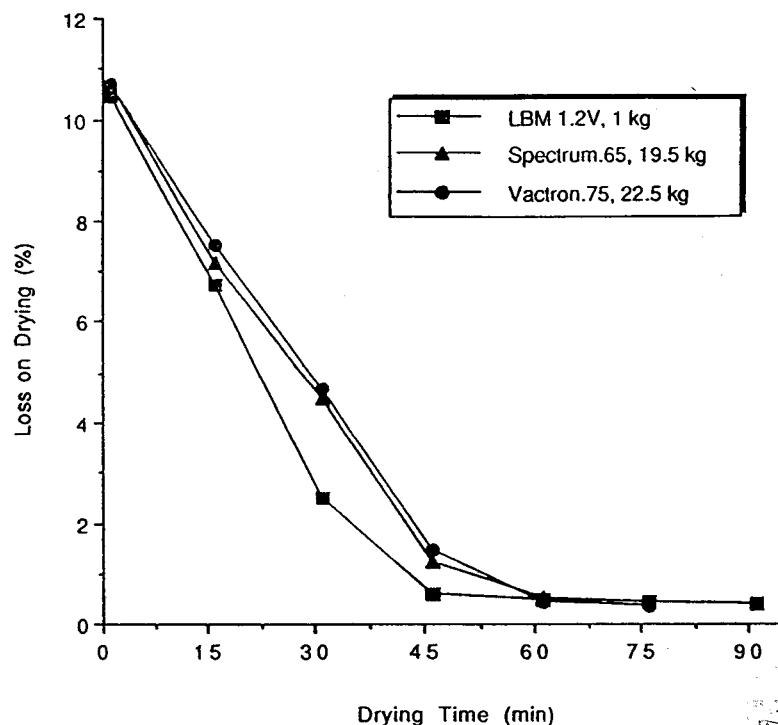
a development- or pilot-scale unit to be aware of the maximum production-scale processor. For example, a 20-kg batch size is available to dry a 20-kg batch size. The Vactron.600 can provide only a 200 kg batch. Table 2 compares the pilot and production-scale units of processors.

drying curves for a 12% aqueous granulation. The Vactron.75 when forward power is the same power capacity. Figure 13 compares vacuum drying and the equivalent curves for a 7% ethanol granulation. The curves are adjusted to assure consistency

**Table 2** Maximum Power Capacities for Microwave-Vacuum Single-Pot Processors

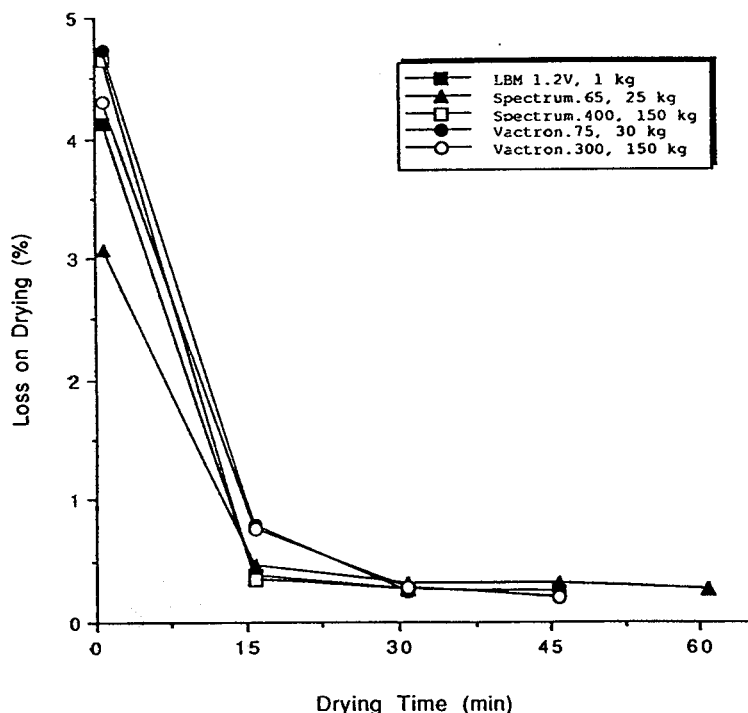
Pilot scale		Production scale	
Processor	MMP <sup>a</sup>	Processor	MMP <sup>a</sup>
Vactron.75	0.25	Vactron.600	0.12
Vacumat.70	0.15	Vacumat.600	0.09
Spectrum.65	0.09	Spectrum.600	0.10

<sup>a</sup>MMP is the maximum microwave power capacity based on drying a 20-kg batch size at the pilot-scale and 200-kg batch at the production-scale.



**Fig. 12** Scalability of microwave-vacuum drying, effect of batch size on drying time (12% aqueous granulation). Note: microwave power output (kW/kg) was the same for all three processors. Vacuum level for each was 40–50 mbar.





**Fig. 13** Scalability of microwave-vacuum drying, effect of batch size on drying time (7% ethanol granulation). Formulation B is an ethanol granulation. Although the batch sizes ranged from 1 to 150 kg and three different scales of microwave dryers were used, drying curves were similar. Same kW/kg and vacuum level as in Fig. 12.

## VI. REGULATORY CONSIDERATIONS

Single-pot processors combine established technologies into a single piece of equipment and, in general, deserve no special regulatory consideration when using them to develop a new product or to manufacture an approved product. Robin and colleagues [2] surveyed eight European regulatory agencies in 1992 to determine the implications of converting from fluid bed drying to microwave-vacuum drying within a single-pot processor. The majority of the agencies required only process validation data, and three suggested limited stability data (up to 6 months of accelerated data). These requests were no different from those expected for similar types of manufacturing changes (i.e., change in process or equipment).

Manufacturers consider immediate-release, solid oral dosage forms as an approved manufacturing process. Regulatory agencies governing the manufacture of these products. For drug products sold in the United States, the FDA's SUPAC IR Guidelines provide postapproval changes for manufacturing changes at levels of change that may be acceptable. It outlines the chemical and physical characterization for each level of change. The filing (Annual Report, Prior Information Statement).

For example, a tablet manufacturer may replace a shear granulator and dried granulation process with a single-pot processor to replace this process with a single-pot processor. This change in granulation and gas-assisted drying is viewed as a change in equipment. The principles (defined as a Level 2 change) are described in the document). Such a change requires a New Drug Approval Supplement, with stability data (depending on the product). The submission must include data including the new equipment profiles.

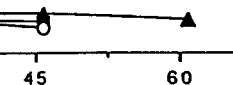
## VII. VALIDATION OF SINGLE-POT PROCESSING

Because single-pot processors combine established technologies into a single processor, their validation requirements are described in sources adequately described in the literature [19], although validation approaches to process control are still being developed.

For operational qualification, the single-pot processor is used in the field, forward power, and air flow rate are monitored by the vendors because of the cost associated with the capital equipment. The cost of microwave systems should be minimized and require no more than the traditional approaches.

When microwave processing is used, the expectation that E-field would be uniform throughout the product. With experience, users found

M 1.2V, 1 kg  
 spectrum.65, 25 kg  
 spectrum.400, 150 kg  
 ctron.75, 30 kg  
 ctron.300, 150 kg



...ing, effect of batch size on drying  
 ...s an ethanol granulation. Although  
 ...three different scales of microwave  
 ...ame kW/kg and vacuum level as in

...technologies into a single piece  
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 ...r equipment).

Manufacturers considering converting to a single-pot process for an immediate-release, solid oral dosage form (tablets, capsules, or the like) with an approved manufacturing process should consult their appropriate regulatory agencies governing the practices they use to manufacture their products. For drug products sold in the United States, manufacturers should refer to FDA's SUPAC IR Guidance document [18] that addresses scale-up and postapproval changes for marketed products. This document describes the levels of change that may be made in a manufacturing process and equipment. It outlines the chemistry, manufacturing, and control tests and documentation for each level of change as well as the appropriate regulatory filing (Annual Report, Prior Approval Supplement, or other).

For example, a tablet formulation is currently granulated using a high shear granulator and dried in a tray drier. A drug manufacturer wishes to replace this process with a single-pot processor that incorporates high shear granulation and gas-assisted vacuum drying. This conversion would be viewed as a change in equipment to a different design and operating principles (defined as a Level 2 Equipment Change in the SUPAC IR Guidance document). Such a change requires the manufacturer to submit a Prior Approval Supplement, with up to three batches with 3-months accelerated stability data (depending on the duration of commercial experience with the product). The submission would also require updated batch records including the new equipment, and the generation of multipoint dissolution profiles.

## VII. VALIDATION OF SINGLE-POT PROCESSORS

Because single-pot processors combine standard engineering approaches into a single processor, their validation should pose no special problems. Other sources adequately describe the validation of granulating and drying processes [19], although validation of the microwave-drying system and the approach to process control of drying endpoint deserves special mention.

For operational qualification of microwave components, such as E-field, forward power, and arc detection, we suggest that customers contract the vendors because of the specialized nature of microwave systems. The cost associated with the calibration equipment is difficult to justify, and microwave systems should operate reliably following proper setup and qualification and require no more periodic maintenance than other granulation approaches.

When microwave processors were first introduced, there was the expectation that E-field would be a reliable indicator of the drying endpoint. With experience, users found that the E-field tends to be too variable, and

now view it primarily as a safety feature monitoring the microwave field within the drying cavity. Product temperature, time, and cumulative forward power are proving more reliable indicators of drying endpoint with verification by some in-process control that directly measures moisture content of a product sample. Industrial processes are in operation today that use one of these three approaches.

## VIII. DATA ACQUISITION SYSTEMS

Users of single-pot processors may use one or all of its processing features (mixing, granulating, drying, or other). The accompanying data acquisition system must collect, display, and record the relevant processing conditions and granulation behavior for each cycle. The degree of sophistication of the system may depend on the venue in which the processor is used. In a development setting, the sequence of cycles is often interrupted to collect samples for analysis, and the user is interested in capturing as much information as possible to assist in defining a suitable processor for a particular formulation. In production, the manufacturing sequence and process parameters are predefined and validated, and information needs are reduced to monitoring critical parameters. For the purposes of trouble-shooting and trend analysis of production operations, however, the information requirements of development and production converge, and data acquisition systems for single-pot processors should seek to address the needs of both types of users.

The following is an outline of a data acquisition system developed for a Spectrum.400 Processor (high shear mixer–granulator with microwave–vacuum-drying capabilities) housed in a pilot plant facility and used for process development and the manufacture of stability and clinical supplies. The system was developed to complement the operator's visual display standardly supplied by the vendor, which consisted of a computer to display processing conditions and a printer to provide a permanent record.

The data acquisition system comprises three components:

1. Process data display and reporting
2. Recipe display and reporting
3. Alarm display and reporting

### A. Process Data Display and Reporting

The following process parameters are monitored during the specified cycles:

1. Blending, granulation, cooling, and lubrication
  - Time (min)

- Impeller speed (rpm)
- Impeller load (kg)
- Total energy consumed (kWh)
- Granulator speed (rpm)
- Granulator load (kg)
- Product temperature (°C)
- Jacket temperature (°C)

### 2. Drying and cooling

- Time (min)
- Impeller speed (rpm)
- Impeller load (kg)
- Product temperature (°C)
- Jacket temperature (°C)
- Forward microwave power (kW)
- Cumulative microwave energy (kWh)
- E-field (%)
- Vacuum (mbar)

### 3. Features

- Data is retrievable, can be manipulated and process data verified, and can be displayed and printed.
- The user is able to interrupt a cycle. For example, a granulation cycle typically takes 10 minutes; a cycle may take a maximum of 15 minutes and does not exceed 15 minutes. The following are the features: blending (1 minute); cooling (1 minute); drying (1 minute); and granulation (1 minute).
- For each cycle, the system automatically collects data. For example, if the drying cycle is interrupted, the process data is collected during the drying interval, but the data is not included in the cycle. This is especially important for cycles that are monitored in a cumulative manner.
- During the granulation cycle, the system monitors the granulation and the product delivery system.
- The data acquisition system records the data for each cycle.

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monitored during the specified cycles:

and lubrication

- Impeller speed (rpm)
  - Impeller load (kW)
  - Total energy consumption of the impeller (kW/h)
  - Granulator speed (rpm)
  - Granulator load (amp)
  - Product temperature (°C)
  - Jacket temperature (°C)
2. Drying and cooling
    - Time (min)
    - Impeller speed (rpm)
    - Impeller load (kW)
    - Product temperature (°C)
    - Jacket temperature (°C)
    - Forward microwave power (kW)
    - Cumulative microwave power consumed (kW/h)
    - E-field (%)
    - Vacuum (mbar)
  3. Features
    - Data is retrievable as a spreadsheet file so that the user can manipulate and model data accordingly. For example, print process data versus time in a tabular format and graphically display and print process parameters versus time.
    - The user is able to set the frequency of data collection for each cycle. For example, a granulating cycle (in a high shear granulator) typically lasts less than a half hour, whereas, a drying cycle may take a couple of hours, and blending and lubrication does not exceed a few minutes. Recommended frequencies are the following: blending (10 s); granulation (10 s); drying (30 s); cooling (1 min); and lubrication (10 s).
    - For each cycle, the elapsed time starts at zero, and the system automatically collects data in a cumulative fashion. For example, if the drying cycle is interrupted several times for sampling, the process does not start at time zero after each sampling interval, but resumes at the time at which it was stopped. This is especially important for those process parameters monitored in a cumulative fashion (e.g., microwave power consumed).
    - During the granulation cycle, there is an indicator that the solvent delivery system is activated.
    - The data acquisition screen can be printed at any time during a cycle.

## B. Recipe Display and Reporting

- Displays recipe data for a particular cycle in a format similar to the display on the operator interface screen.
- Recipe includes pressure setting for delivery of granulating solution, because this is not indicated on the vendor's operator interface screen or printout. (Note that this is available on subsequent data acquisition systems offered by the vendor.)
- The data acquisition screen can be printed at any time during a cycle.

## C. Alarm Display and Reporting

- Displays individual alarms on the operator interface as they occur during processing.
- Displays and prints a summary table of alarms which have occurred during a specified process cycle or time period.

## IX. SAFETY

The primary safety concern during the granulation and drying processes is the prevention of explosions. Bulk powder, dust clouds, and flammable vapors, all have the potential to explode. Adequate grounding and ventilation during loading and discharging the vessel and controlling the various processing conditions can reduce the risk of explosion. Dryers should be designed to either contain an explosion or possess a release panel through which a fire ball could be vented. At the conclusion of drying, the vacuum may be broken through the addition of an inert gas, reducing the risk of explosion by the removal of oxygen from the chamber.

The leakage of microwave energy is a concern for single-pot processors that use this drying approach. Industrial microwave processors are expected to meet the guidelines for microwave leakage specified by the Center for Devices and Radiological Health within FDA and by the American National Standards Institute [20,21]. The guideline is 5 mW/cm<sup>2</sup> maximum exposure at a frequency of 2450 MHz at a distance of 5 cm from any surface of the microwave cavity. Survey meters for the detection of microwave leakage are relatively inexpensive and should be purchased by users of single-pot processors that incorporate microwave drying. The survey meters are calibrated before shipment and returned to the supplier for recalibration at periodic intervals. Their use should be incorporated in standard operating procedures for the equipment. Operator readings that exceed the guideline limit are often indicative of deteriorating seals around the lid cavity.

In addition to energy le signed with safety interlocks the magnetrons can be activ the processor) is operating u uum falls outside this range, ertently tries to open the li netrons are disabled. Vend assure the microwave power

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## X. FUTURE

Single-pot processing enjoys processing. It is often the te ulations (e.g., effervescent fo tal conditions and benefit fro last few years, equipment v tractive to potential customer tings. Single-pot processors facture small-scale batches 1000 g) and are also availab

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In addition to energy leakage standards, microwave processors are designed with safety interlocks to prevent accidental exposure. For example, the magnetrons can be activated only if the microwave cavity (i.e., bowl of the processor) is operating under vacuum, usually 45–100 mbar. If the vacuum falls outside this range, as in the unlikely event that an operator inadvertently tries to open the lid during microwave–vacuum drying, the magnetrons are disabled. Vendors also incorporate additional safeguards to assure the microwave power is disabled with access to the bowl.

Because of popular misconceptions about the use of microwave ovens (e.g., stainless steel should not be used in a microwave cavity) and electromagnetic radiation (e.g., all types cause biological effects), a training program should be instituted in any facility that uses microwave drying. This will demystify any unfounded concerns about the technology and foster a rational approach to a sound safety and maintenance program.

## X. FUTURE

Single-pot processing enjoys a distinct and vibrant niche in pharmaceutical processing. It is often the technology of choice for moisture-sensitive granulations (e.g., effervescent formulations) that require controlled environmental conditions and benefit from a minimum of material transfer steps. In the last few years, equipment vendors have provided a variety of options attractive to potential customers in both the development and production settings. Single-pot processors are now available in sizes sufficient to manufacture small-scale batches required in the early development stage (300–1000 g) and are also available with a variety of drying and cooling options.

Single-pot processors offering microwave drying still suffer from misconceptions concerning excessive regulatory scrutiny and difficulties with validation. Gas-assisted vacuum-drying technology may offer cost and installation advantages for certain customers. However, we believe that the negative concerns for microwave technology are unfounded, and prospective buyers should objectively determine the cost/benefit ratio of the various drying options that vendors now offer.

Single-pot technology, in general, suffers from a lack of publications in the pharmaceutical literature. Because of the long development time and high cost for new products, and a conservative atmosphere spawned by strict regulatory controls, development and production personnel naturally follow the path of least resistance when selecting granulation technologies. This intransigence may be overcome if more papers were published in the area of single-pot processing that addressed areas such as validation, and the

interaction between the granulation and drying operations on particle morphology and size.

Nevertheless, single-pot processing will continue to maintain a presence in granulation technology because of the current level of interest in containment systems. As pharmaceutical companies develop more potent and toxic compounds in an atmosphere of increasing concern for operator and environmental safety, the potential advantages of single-pot processing relative to other alternatives will continue to be explored. Additionally, as primary manufacturing of drug substance undergoes conversion to operate under good manufacturing practices, the capability of single-pot processing to serve as reaction vessels during various stages of drug synthesis may expand its market demand.

### ADDITIONAL INFORMATION

The International Microwave Power Institute (13542 Union Village Circle, Clifton VA 22024) offers introductory and specialized courses on microwave technology at its annual meetings. Although not oriented to the processing of pharmaceuticals, the introductory course is a useful orientation for anyone intending to apply the technology to granulation technology.

### REFERENCES

1. LJ Lucisano, RP Poska. Microwave technology—fad or the future. *Pharm Technol* 14:38–42, 1990.
2. P Robin, LJ Lucisano, DM Pearlszig. Rationale for the selection of a single pot manufacturing process using microwave/vacuum drying. *Pharm Technol* 18:28–36, 1994.
3. G Bellini, L Pellegrini. Non adiabatic drying. In: *Handbook of Downstream Processing*, 1993.
4. P DeSmet. Vacuum drying. *Manuf Chem* March:37–39, 1989, p. 37.
5. Technical Report. Granulation and drying with SYSTEM-VAGAS. LB Bohle, Inc., Bristol PA 19007.
6. Technical Report. AEROVAC system, accelerated vacuum drying. Niro-Fielder Ltd., Eastleigh, Hampshire, United Kingdom.
7. AC Metaxas, RJ Meredith. *Industrial Microwave Heating*. London: Peter Peregrines, 1983.
8. C Doyle, MJ Cliff. Microwave drying for highly active pharmaceutical granules. *Manuf Chem* Feb:23–32, 1987.
9. MS Waldron. Microwave vacuum drying of pharmaceuticals: the development of a process. *Pharm Eng* 8:9–13, 1988.

10. RP Poska. Microwave processing. In: *Proceedings of International Symposium on Microwave Processing*, September 1992.
11. LJ Lucisano, RA Moss. Vacuum assisted single pot process for granulation. *AAPS Annual Meeting*, 1994.
12. TK Mandal. Evaluation of microwave drying. *Drug Dev Ind Pharm* 21:1–10, 1994.
13. RA Moss. Demonstration of single pot processing. *AAPS Annual Meeting*, Washington DC, 1994.
14. R Poska. Integrated mixing and drying: experience. *Pharm Eng* 11:1–10, 1994.
15. K Van Scoik. Microwave vacuum drying. *AAPS Annual Meeting*, Washington DC, 1994.
16. G Duschler, W Carius, KH Duschler. Microwave drying of pharmaceuticals: preliminary studies. *Pharm Eng* 15:1599–1610, 1995.
17. DM Pearlszig, P Robin. Microwave assisted drying: development of a single-pot process. *Pharm Technol* 18:44–60, 1994.
18. FDA. Immediate release solid oral dosage forms: changes: chemistry, manufacturing, and controls. *FDA Center for Drug Evaluation and Research*, 1995.
19. IR Berry, RA Nash, eds. *Pharmaceutical Technology*. Dekker, 1993.
20. Performance standards for microwave drying. *21 Code of Federal Regulations*, 1 April 1994.
21. Electromagnetic fields, safety. *ANSI C95.1-1991*. Institute, 1992, pp. 9–10.

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with SYSTEM-VAGAS. LB Bohle,

lerated vacuum drying. Niro-Fielder  
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rowave Heating. London: Peter Per-

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10. RP Poska. Microwave processing: the development experience revisited. Proceedings of International Society of Pharmaceutical Engineers Congress, September 1992.
11. LJ Lucisano, RA Moss. Vacuum drying vs. microwave–vacuum drying in three pilot-scale single pot processors using sodium acid pyrophosphate as the model granulation. AAPS Annual Meeting, San Antonio, Texas, Nov 15, 1992.
12. TK Mandal. Evaluation of microwave drying for pharmaceutical granulations. Drug Dev Ind Pharm 21:1683–1688, 1995.
13. RA Moss. Demonstration—microwave/vacuum drying of pharmaceuticals. AAPS Annual Meeting, Washington DC, Nov 17, 1991.
14. R Poska. Integrated mixing granulating and microwave drying: a development experience. Pharm Eng 11:9–13, 1991.
15. K Van Scoik. Microwave vacuum processing in the Vactron 300. AAPS Annual Meeting, Washington DC, November 1991.
16. G Duschler, W Carius, KH Bauer. Single-step granulation method with microwaves: preliminary studies and pilot scale results. Drug Dev Ind Pharm 21: 1599–1610, 1995.
17. DM Pearlswig, P Robin, LJ Lucisano. Simulation modeling applied to the development of a single-pot process using microwave/vacuum drying. Pharm Technol 18:44–60, 1994.
18. FDA, Immediate release solid oral dosage forms: scale-up and postapproval changes: chemistry, manufacturing, and controls; in vitro dissolution testing; in vivo bioequivalence documentation; guidance. Fed Reg 60:61638–61643, 1995.
19. IR Berry, RA Nash, eds. Pharmaceutical Process Validation. New York: Marcel Dekker, 1993.
20. Performance standards for microwave and radio frequency emitting products. 21 Code of Federal Regulations, Part 1030. Washington, DC: General Services Administration, 1 April 1988, pp. 461–464.
21. Electromagnetic fields, safety levels with respect to human exposure to radio frequency (ANSI C95.1-1982). New York: American National Standards Institute, 1982, pp. 9–10.



# 11

## Extrusion—Spheronization as a Granulation Technique

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## I. INTRODUCTION

Extrusion-spheronization is a multiple step process capable of making uniformly sized spherical particles. It is primarily used as a method to produce multiparticulates for controlled-release applications. The major advantage over other methods of producing drug-loaded spheres or pellets is the ability to incorporate high levels of active components without producing an excessively large particle. Although the process is more efficient than other techniques for producing spheres, it is more labor- and time-intensive than the more common granulation techniques. Therefore, it should be considered as a granulating technique when the desired particle properties are essential and cannot be produced using more conventional techniques.

Spheronization is a process invented by Nakahara, in 1964. The patent describes a *Method and Apparatus for Making Spherical Granules* from wet powder mixtures [1]. The equipment described in the patent was commercialized by Fuji Denki Kogyo Co. under the trade name Marumerizer. The process went widely unnoticed in the pharmaceutical industry until 1970, when two articles were published by employees of Eli Lilly & Co. Conine and Hadley [2] described the steps involved in the process, including (a) dry blending, (b) wet granulation, (c) extrusion, (d) spheronization, (e) drying, and (f) screening (optional). Reynolds [3] went on to further describe the equipment and the mechanics of the process, including the movement of the particles within the spheronizer. Both publications cite desirable product attributes that can be achieved, including good flow, low dusting, uniform size distribution, low friability, high hardness, ease of coating, and reproducible packing. From the publication of these articles through to today, the interest in extrusion-spheronization has continued to grow. The process has recently become established in industry, but was primarily driven by academia in the interim. The increased popularity in recent years is, in part, due to a growing understanding of the effects of process parameters and material characteristics.

## II. APPLICATIONS

Potential applications are many, including both immediate- and controlled-release dosage forms. Two or more active agents can easily be combined in any ratio in the same unit. These combination products can contain active agents that are incompatible or have varying release profiles. Spheres can be used as a method to limit drug migration. Physical characteristics of the active ingredients and excipients can be modified to improve physical properties and downstream processing. As an example, a low-density, finely di-

vided active component can and limit dusting [4]. Functionally. Dense multiparticulate tract and can be used to p improve tolerance of some must be taken to achieve th

Spheres for controlled substantially different physical A product to be coated for distribution, good sphericity ability. Once coated, the sp istics. Additionally, if the co they will require sufficient s After disintegration of the original release profile. Phys porosity, and surface area, b pression into tablets. The gr ing characteristics to form ta release from the final dosag

Products produced by barely shaped, irregular part ventional granulation, to ve drastically different [7]. Tabl either the composition of [9], or the process conditions conducted on spheres simil tions show the bonding an spheronization can alter the [9]. Microcrystalline cellul powder state, exhibits elasti spheronized [8]. The deform sized particles result in few compacts. A compaction pr is shown in Fig. 1. The poi each application, but rather, have very specific requirem required and then tailor the of process and formulation

A review of the literat understand small componen They have focused on part valuable to have a detailed

process capable of making uniformly used as a method to produce granulations. The major advantage of spheres or pellets is the ability to produce uniform granules without producing an excessive amount of fines. This process is more efficient than other granulation processes, which are labor- and time-intensive than extrusion. Therefore, it should be considered that uniform granule properties are essential for the success of granulation techniques.

Y. Nakahara, in 1964. The patent for *Producing Spherical Granules* from wet granulation was described in the patent with the trade name Marumerizer. The Marumerizer was used in the pharmaceutical industry until 1970, when it was replaced by the Conine process of Eli Lilly & Co. Conine process, including (a) extrusion, (d) spheronization, (e) dry granulation. [3] went on to further describe the process, including the movement of granules. Several publications cite desirable producing good flow, low dusting, uniformity, low hardness, ease of coating, and the use of these articles through to today, the process has continued to grow. The process has been improved, but was primarily driven by the need for uniformity in recent years is, in part, the effects of process parameters and

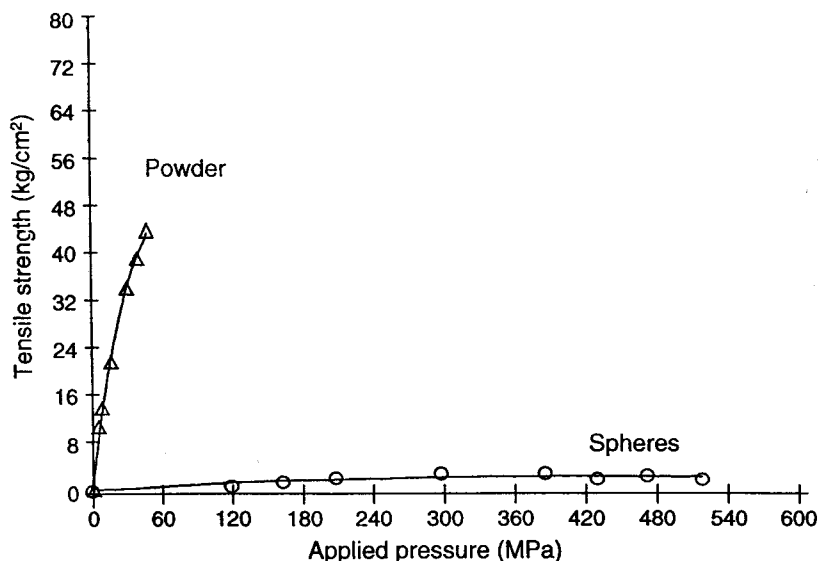
both immediate- and controlled-release granules can easily be combined in granulation products can contain active ingredients and release profiles. Spheres can be used for controlled release. Physical characteristics of the granules can be modified to improve physical properties. For example, a low-density, finely di-

vided active component can be pelletized to increase density, improve flow, and limit dusting [4]. Functional coatings can be applied easily and effectively. Dense multiparticulates disperse evenly within the gastrointestinal tract and can be used to prolong gastrointestinal transit times [5,6] or to improve tolerance of some compounds. Regardless of the application, care must be taken to achieve the required sphere or granule properties.

Spheres for controlled-release-coating applications will likely have substantially different physical requirements than granules for compression. A product to be coated for controlled-release should have a uniform size distribution, good sphericity and surface characteristics, as well as low friability. Once coated, the sphere should have the desired release characteristics. Additionally, if the coated spheres are to be compressed into tablets, they will require sufficient strength to withstand the forces of compression. After disintegration of the tablet, the individual spheres must retain their original release profile. Physical properties, such as flow, density, friability, porosity, and surface area, become important for granules intended for compression into tablets. The granules should have good deformation and bonding characteristics to form tablets having desirable physical properties. Drug release from the final dosage form must meet the target specification.

Products produced by using extrusion-spheronization can range from irregularly shaped, irregular particles with physical properties similar to a conventional granulation, to very spherical particles having properties that are drastically different [7]. Tableting characteristics can be modified by altering either the composition of the spherical particles [8], granulating fluid [9], or the process conditions used to produce them [10]. Compaction studies conducted on spheres similar to those used for controlled-release applications show the bonding and densification that occur during extrusion-spheronization can alter the deformation characteristics of some materials [9]. Microcrystalline cellulose (MCC), which deforms plastically in the dry powder state, exhibits elastic deformation followed by brittle fracture once spheronized [8]. The deformation characteristics, coupled with the larger-sized particles result in fewer bonding sites and the production of weak compacts. A compaction profile of MCC and spheres prepared from MCC is shown in Fig. 1. The point is not to dwell on the properties required for each application, but rather, to reinforce the fact that each application will have very specific requirements. One must first understand the properties required and then tailor the process to yield the desired effects. The effects of process and formulation variables will be discussed later.

A review of the literature shows that most investigators have tried to understand small components of this process, isolated from other effects. They have focused on particular formulation or process parameters. It is valuable to have a detailed understanding of the main variables; however,



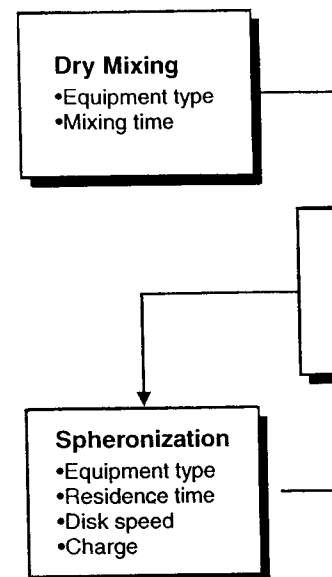
**Fig. 1** Compaction profiles of microcrystalline cellulose powder and spheres. (From Ref. 8.)

this approach fails to take into consideration the high degree of interaction that exists between the variables. The use of statistical experimental design is a valuable tool to understand not only the main effects, but also the interactions that can have a profound effect on the characteristics of the resulting particles [11–13]. Additionally, these techniques are extremely useful during product and process development to understand the effect of variables and be able to control them to produce a product having desired attributes [14]. After pointing out the benefits of design methodology in this application, it should be understood that, for simplicity, much of the discussion to follow will address the various topics individually. In reality, however, they truly cannot be isolated from one another. This chapter will review and discuss the general process, equipment types, and the effect of process and formulation variables on the properties of spherical granules.

### III. GENERAL PROCESS DESCRIPTION

Extrusion–spheronization is a process requiring at least five units of operation with an optional sixth screening step. First, the materials are dry mixed (a) to achieve a homogeneous powder dispersion and then wet granulated

### Extrusion–Spheronization



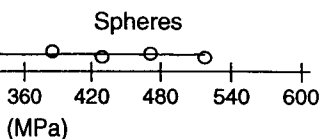
**Fig. 2** Process flow chart of extrusion-spheronization. Critical process variables for each individual step are shown.

(b) to produce a sufficiently homogeneous powder dispersion to form rod-shaped particles in the extruder. The extruded particles are then dried (e) to achieve a desired moisture content. The dried particles are then screened (f) to achieve a desired particle size distribution. The process flow diagram, shown in Fig. 2, illustrates the general process along with critical variables for each step. The critical variables for each of the steps is shown in Table I.

## IV. EQUIPMENT DESCRIPTION AND PARAMETERS

### A. Dry Mixing

During the first step, powder is dry mixed before wet granulation. It is important to select the right mixer for the granulation; however, a V-blender or a ribbon mixer is required for the dry mixing because wet massing follows

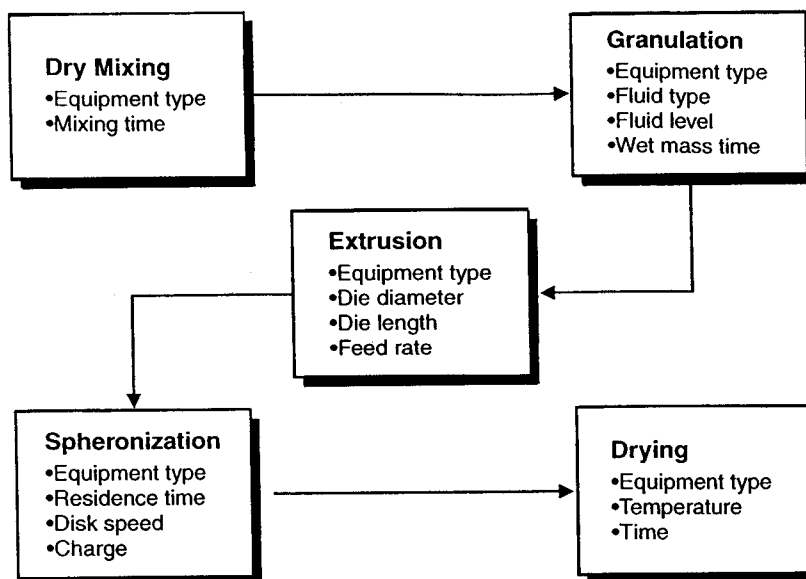


lline cellulose powder and spheres.

on the high degree of interaction of statistical experimental design y the main effects, but also the fect on the characteristics of the hese techniques are extremely use- nt to understand the effect of var- roduce a product having desired fts of design methodology in this for simplicity, much of the dis- us topics individually. In reality, m one another. This chapter will quipment types, and the effect of properties of spherical granules.

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quiring at least five units of oper- First, the materials are dry mixed spersion and then wet granulated



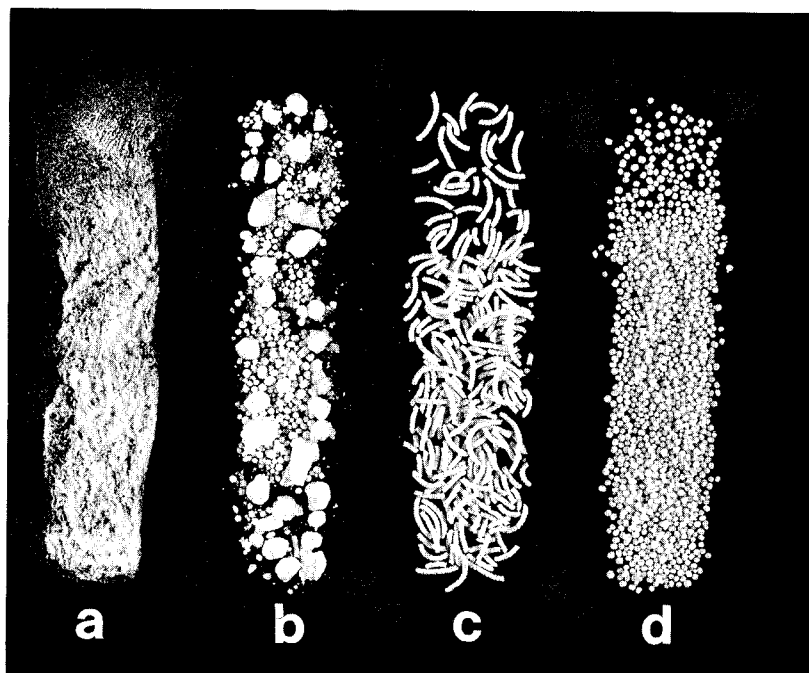
**Fig. 2** Process flow chart of the extrusion-spheronization process showing the process variables for each individual step. (From Ref. 15.)

(b) to produce a sufficiently plastic wet mass. The wet mass is extruded (c) to form rod-shaped particles of uniform diameter that are charged into a spheronizer and rounded off (d) into spherical particles. The spherical particles are then dried (e) to achieve the desired moisture content and optionally screened (f) to achieve a targeted size distribution. The process flow diagram, shown in Fig. 2, has been used to show each of the process steps along with critical variables associated with them [15]. The end product from each of the steps is shown in Fig. 3.

#### IV. EQUIPMENT DESCRIPTION AND PROCESS PARAMETERS

##### A. Dry Mixing

During the first step, powders are dry mixed to achieve a uniform dispersion before wet granulation. It is generally carried out in the same mixer used for the granulation; however, if a continuous granulator is used, a separate mixer is required for the dry mix. This step is typically taken for granted because wet massing follows. The uniformity of the dry mix, however, can



**Fig. 3** Product produced by the first four extrusion-spheronization process steps: (a) powder from dry mixing, (b) granules from granulation, (c) extrudate from extrusion, and (d) spheres from spheronization.

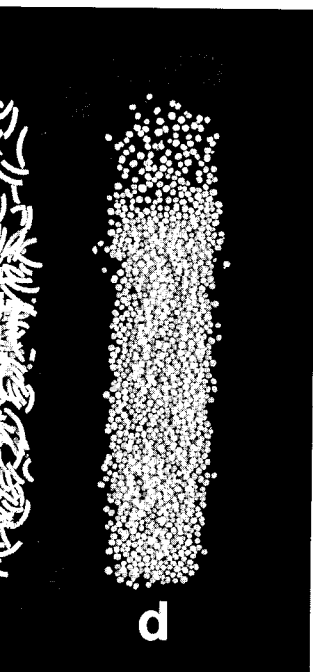
have a significant effect on the quality of the granulation and, in turn, on the spherical particles produced. An uneven distribution of materials having wide differences in properties, such as size and solubility, can result in localized overwetting, at least initially, during the granulation step. The more soluble and finely divided components can also dissolve and become part of the granulating fluid. The fluids, rich in soluble compounds, can either remain as overwet regions or, with continued wet massing, can be redistributed [16]. Sphere uniformity (size and shape) is very much dependent on the uniform distribution and composition of the granulating fluid, which includes not only the solvent, but also any dissolved ingredients.

## B. Granulation

The second step is granulation, during which a wet mass, having the requisite plasticity or deformation characteristics, is prepared. With a few ex-

ceptions, this step is similar to the first step, in which the materials are mixed to produce products for compression. The mixer-granulator; however, produces a wet mass, including the continuous addition of liquid. Examples of mixers used in granulation include planetary mixers, vertical mixers, and paddle blade mixers. Examples of extruders used in granulation include the mixer [17] and high shear mixer. The high shear mixer consists of a rapidly rotating rotor that mixes the mixture and granulating fluid. The granulating zone or chamber and the feed rate of the powder are controlled. The high shear twin-screw mixer is also used. It consists of shearing and kneading the mixture in through separate ports and ports for the screws. The mixer-extruder is used to control the amount of shear and energy input. The duration of the mixing blades and the speed of the extrudate produced [18] are controlled to achieve a uniform level of moisture. The solids ratio is accomplished by the ratio of the solids into the mixer-extruder. Both steps are the most problematic. Small variations in the moisture content of the materials can result in spherical particles produced.

The two major differences between the typical granulations for compression and extrusion are the required and the importance of the fluid. The amount of fluid needed to granulate is likely to be greater than the amount needed for extruding. Instruments such as a moisture analyzer have been used to characterize the moisture in use in extrusion-spheronization. The rheological effect of formulation is also important. The ram extruder has been used to produce a state flow, during which the materials are in a state of flow, during which the materials are in a state of flow, and (c) forced flow, during which the materials are in a state of flow. The three stages are shown in Fig. 4. The change from state of flow to forced flow under pressure is less likely to occur in this phenomenon is less likely to occur.



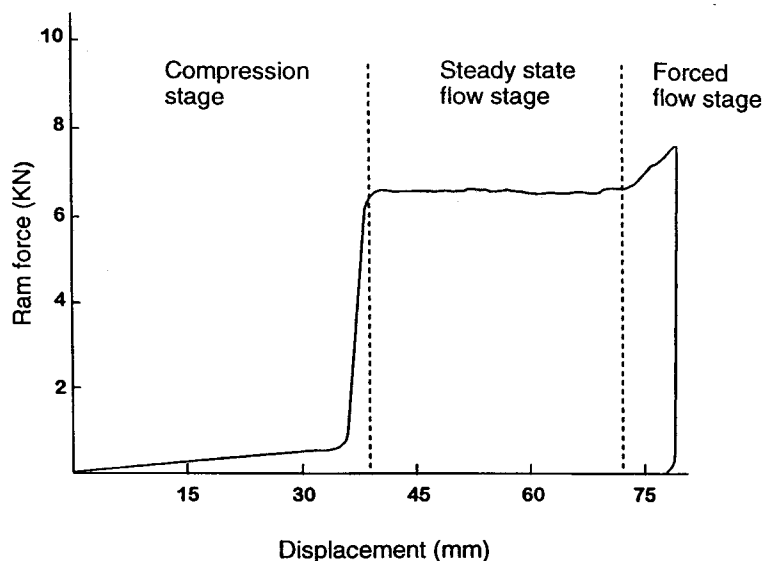
Extrusion-spheronization process steps:  
(a) granulation, (c) extrudate from ex-

the granulation and, in turn, on the distribution of materials having different solubility, can result in long delays during the granulation step. The more soluble compounds, can either dissolve and become part of the granulating fluid, which dissolved ingredients.

which a wet mass, having the required moisture, is prepared. With a few ex-

ceptions, this step is similar to conventional granulation techniques used to produce products for compression. It is typically carried out in a batch-type mixer-granulator; however, any equipment capable of producing a wet mass, including the continuous type, can be used. Batch-type processors include planetary mixers, vertical or horizontal high shear mixers, and sigma blade mixers. Examples of continuous mixers include the Nica M6 instant mixer [17] and high shear twin-screw mixer-extruders [18]. The instant mixer consists of a rapidly rotating disk or turbine onto which the powder mixture and granulating fluid are continuously fed. The charge in the granulating zone or chamber and, therefore, shear can be controlled by adjusting the feed rate of the powder and fluid or the gap of the granule outlet. The high shear twin-screw mixer-extruders have mixer-feeders that are capable of shearing and kneading the feed materials. Dry powders and fluids are fed in through separate ports and mixed by the action of the extruder blades and screws. The mixer-extruder is capable of being configured to customize the amount of shear and energy used in the process by changing the configuration of the mixing blades. This can have an influence on the properties of the extrudate produced [19]. As with the batch processors, it is critical to achieve a uniform level of fluid within the wet mass. The proper fluid/solids ratio is accomplished by maintaining a steady powder and fluid feed into the mixer-extruder. Both are critical; however, the powder feed is the most problematic. Small variations in feed rates can cause significant shifts in the moisture content of the granulation and, therefore, the quality of the spherical particles produced.

The two major differences in the granulation step, as compared with typical granulations for compression, are the amount of granulating fluid required and the importance of achieving a uniform dispersion of the fluid. The amount of fluid needed to achieve spheres of uniform size and sphericity is likely to be greater than that for a similar granulation intended for tableting. Instruments such as a ram extruder [20] and a torque rheometer [21] have been used to characterize the flow characteristics of granulations for use in extrusion-spheronization. They are useful tools in quantifying the rheological effect of formulation and process variations in the granulation. The ram extruder has been used to characterize the flow of wet masses through a die, which has been divided into stages. They are (a) compression, during which the materials are consolidated under slight pressure; (b) steady-state flow, during which the pressure required to maintain flow is constant; and (c) forced flow, during which an increase in force is required to maintain flow. The three stages are shown in the force versus displacement profile in Fig. 4. The change from steady-state to forced flow is caused by the movement of fluid under pressure. Extrusion in a ram extruder is continuous, and this phenomenon is less likely to be seen in extruders that are discontinuous,



**Fig. 4** A force displacement profile for a microcrystalline cellulose-lactose-water mixture showing the three stages of extrusion on a ram extruder: compression, steady-state flow, and forced flow (ram speed,  $4 \text{ mm s}^{-1}$ ; die diameter, 1.5 mm; R/L ratio, 12). (From Ref. 26.)

such as gravity-fed models [22]. A diagram of a ram extruder is shown in Fig. 5.

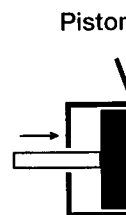
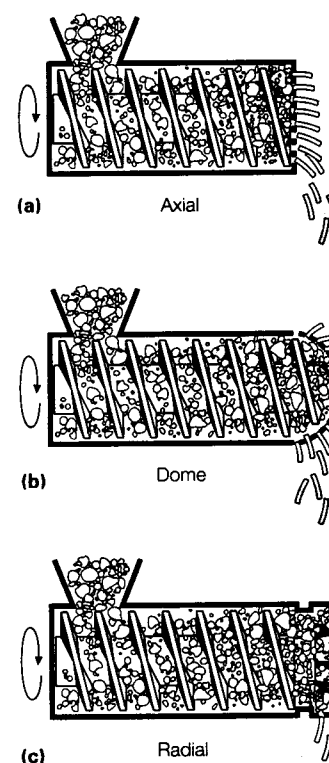
Regardless of the mixer used, one must remember that the downstream process steps of extrusion and spheronization are very dependent on the level of water contained in the granulation and the quality of its dispersion. High-energy mixers, such as high shear mixers and high shear twin-screw mixer-extruders, can cause a significant rise in temperature. It may be necessary to use a jacket to guard against the heat buildup. High temperatures can result in a greater than tolerable level of evaporation [23] or an increase in the solubility of some of the solids. A reduction in fluid will reduce the plasticity of the granulation, whereas an increase in solubility will increase the weight ratio of granulating fluid because the solute is then part of that fluid [24].

### C. Extrusion

The third step is the extrusion step that forms the wet mass into rod-shaped particles. The wet mass is forced through dies and shaped into small cylin-

## Extrusion-Spheronization

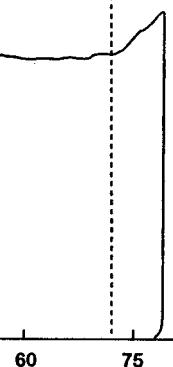
### Screw Feed Extruders



**Fig. 5** Schematic diagrams of



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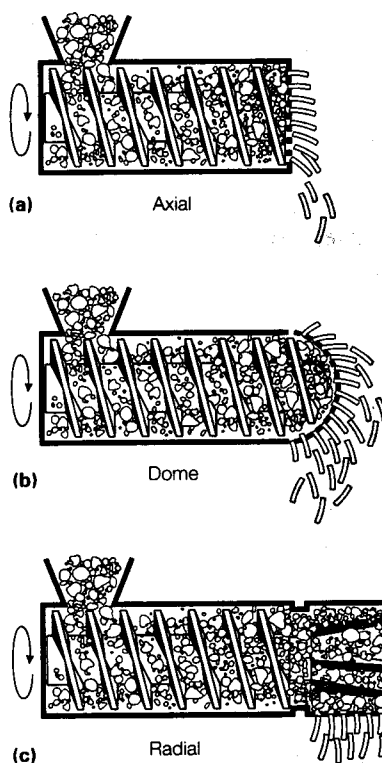
ocrystalline cellulose-lactose-water  
n on a ram extruder: compression,  
4 mm s<sup>-1</sup>; die diameter, 1.5 mm;

n of a ram extruder is shown in

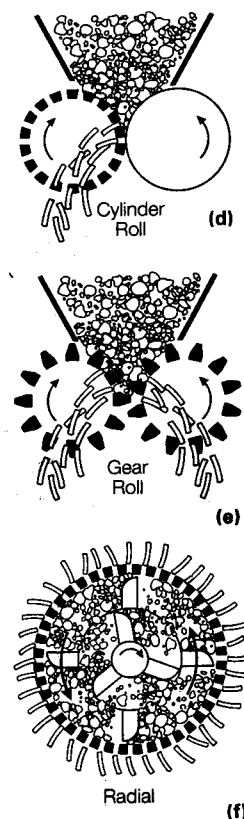
st remember that the downstream  
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e quality of its dispersion. High-  
nd high shear twin-screw mixer-  
temperature. It may be necessary  
buildup. High temperatures can  
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### Screw Feed Extruders



### Gravity Feed Extruders



### Piston Feed Extruder

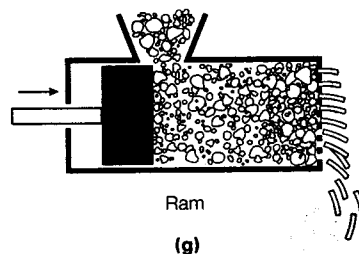


Fig. 5 Schematic diagrams of extruder types used in extrusion-spheronization.

drical particles having a uniform diameter. The extrudate particles break at similar lengths under their own weight. The extrudate must have enough plasticity to deform, but not so much that it adheres to other particles when collected or rolled in the spheronizer.

Extruders come in many varieties, but can generally be divided into three classes, based on their feed mechanism. They include those that rely on a screw, gravity, or a piston to feed the wet mass into the extrusion zone [25]. Examples of extruders from each class are shown in Fig. 5. Screw-feed extruders include the (a) axial or endplate, (b) dome, and (c) radial type, and gravity-feed extruders include (d) cylinder, (e) gear, and (f) radial types. The screw and gravity-fed types are used for development and manufacturing with the radial varieties being the most popular for pharmaceutical applications. The piston feed or ram extruder (g) is primarily used in research as an analytical tool.

Screw extruders have either one (single) or two (twin) augers that transport the wet mass from the feed area to the extrusion zone. During the transport process, the screws compress the wet mass, removing most of the entrapped air. Studies have been conducted on the ram extruder to understand this compression or consolidation stage. They have shown that the apparent density of the wet mass plug before extrusion is approximately equal to the theoretical apparent particle density, indicating that nearly all of the voids were eliminated [26]. Twin-screw extruders generally have a higher throughput than single-screw models, whereas single-screw extruders compress and increase the density of the extrudate more. Other features that can affect the density of the extrudate are the spacing of the turnings on the screw and the space between the end of the screw and the beginning of the die [27]. Turnings that are wide and regularly spaced minimize the amount of compression during material transport. Screws with closer or progressively closer spacing between the turnings will result in more compression and produce a denser extrudate. Space between the screw and the die results in a void into which material is deposited and compressed. The greater the space, the more compression takes place before extrusion. As material builds up, pressure increases and causes the material to be forced, under hydraulic pressure, to flow through the die. When space between the screw and the die is at a minimum, extrusion takes place as material is compressed in the nip, between the extruder blade and the die.

The primary difference between the various types of screw extruders is in the extrusion zone. An axial or dome extruder transports and extrudes the wet mass in the same plane. Axial extruders force the wet mass through a flat, perforated endplate, typically prepared by drilling holes in a plate. The thickness of the plate can be more than four times the hole diameter, resulting in high die length/radius (R/L) ratios. A Luwa axial extruder is

shown in Fig. 6. Dome extruders force the wet mass through the die as the die. It is prepared by a similar process to the hole diameter, but with a higher or lower ratio. A Luwa dome extruder is similar to the axial extruder, but the material is forced through the die by pressure. A radial extruder is shown in Fig. 7. It is forced through the die by pressure. A stamped screen. Because of the number of holes or dies, dome extruders have a higher throughput than the axial types.

As with almost every extruder, the material being extruded during extrusion is a significant factor. Screw-fed extruders. Axial extruders. Radial extruders can have a high throughput. The screen. Materials fed in. The temperature. However, as material is fed, the temperature increases owing to the friction. In feed extruders, the dome type extruder generate significant heat over



Fig. 6 A Luwa axial endplate.



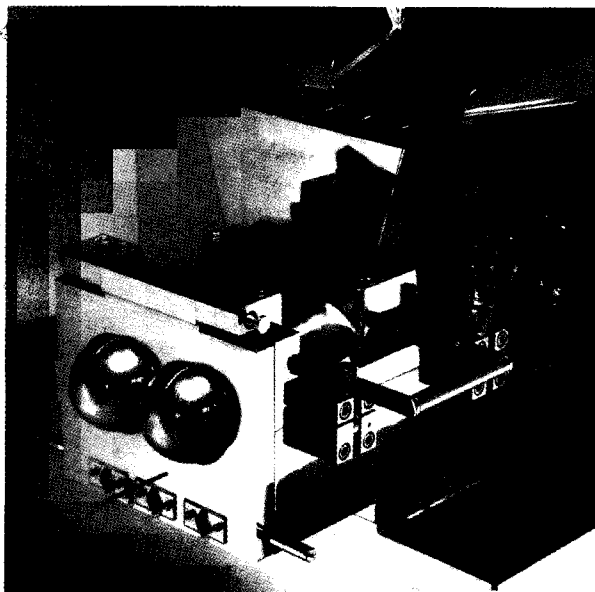


Fig. 7 A Luwa dome extruder. (Courtesy of LCI Corp.)

Gravity-feed extruders include a cylinder, gear, and radial type. The cylinder and gear both belong to a broader class, referred to as roll extruders. Both use two rollers to exert force on the wet mass and form an extrudate. The cylinder extruder has rollers in the form of cylinders: one solid and one hollow with drilled holes to form the dies. The wet mass is fed by gravity into the nip area between the two cylinders and forced through the dies into the hollow of the cylinder. Gear-type extruders have rollers in the form of hollow gears. The dies are holes drilled at the base of each tooth. Wet mass is forced through the holes and collected in the hollow of the gears as the teeth and the base areas mesh. The last type of gravity-feed extruder to be discussed is the radial type. One or more arms rotate to stir the wet mass as it is fed by gravity. Rotating blades wipe the mass against the screen, creating localized forces sufficient to extrude at the nip. There is no compression before extrusion, which is the major difference between the gravity- and screw-feed radial extruders. A Nica extruder is shown in Fig. 9.

The primary extrusion process variables are the feed rate, die opening, and die length. The water content of the granulation is also very critical, because the properties of the extrudate and resulting spheres are very dependent on the plasticity and cohesiveness of the wet mass. The process variables and water content have been the focus of many studies. Harrison

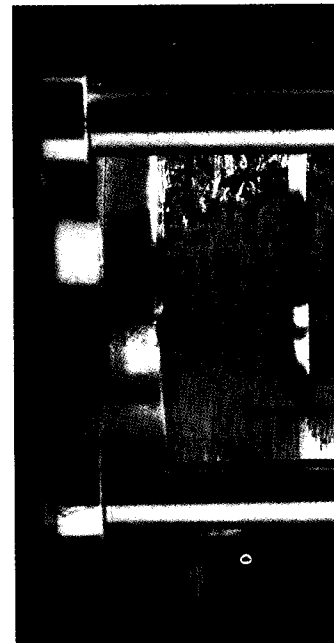
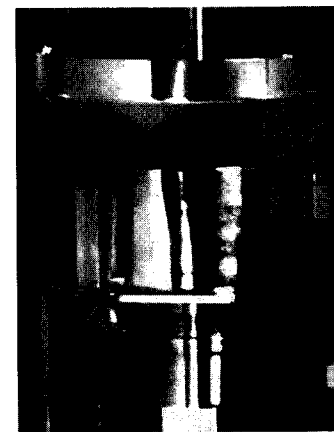


Fig. 8 Side view of the extrusion zone. (Courtesy of LCI Corp.)

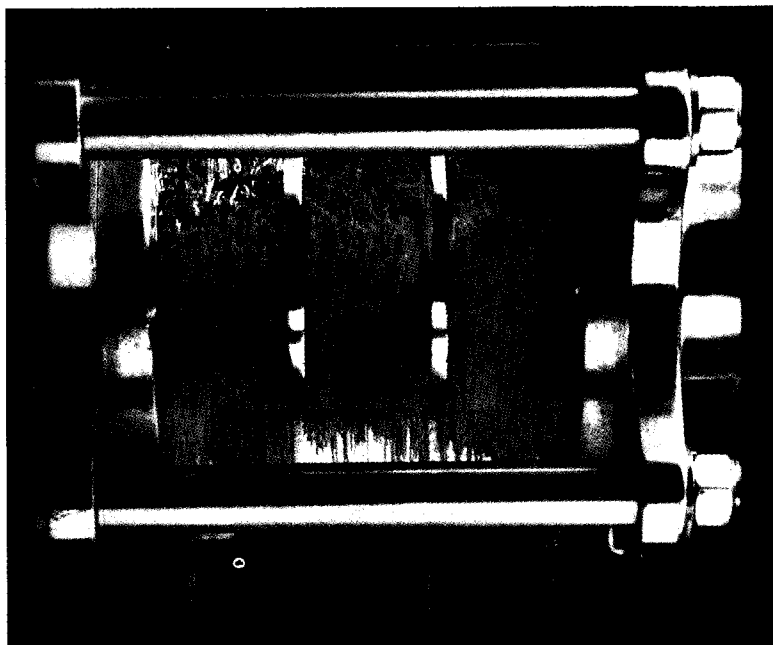


(a)  
Fig. 9 (a) Front view of a Nica extruder. (Courtesy of LCI Corp.)

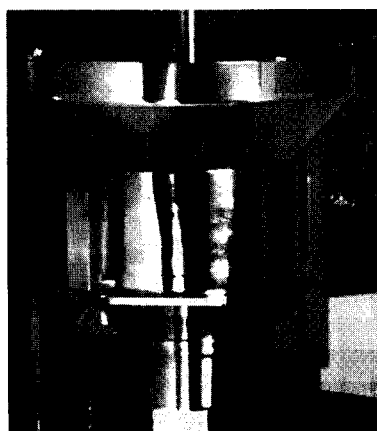


(LCI Corp.)

inder, gear, and radial type. The class, referred to as roll extruders. wet mass and form an extrudate. n of cylinders: one solid and one. The wet mass is fed by gravity and forced through the dies into. nders have rollers in the form of the base of each tooth. Wet mass in the hollow of the gears as the e of gravity-feed extruder to be arms rotate to stir the wet mass ipe the mass against the screen, de at the nip. There is no com- or difference between the gravity- truder is shown in Fig. 9. es are the feed rate, die opening, granulation is also very critical, d resulting spheres are very de- s of the wet mass. The process focus of many studies. Harrison



**Fig. 8** Side view of the extrusion zone of a Luwa screw-feed radial extruder. (Courtesy of LCI Corp.)



(a)



(b)

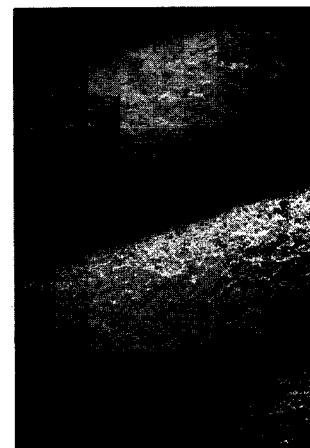
**Fig. 9** (a) Front view of a Nica gravity-feed radial extruder; (b) close-up showing the extrusion zone. (Courtesy of Niro Inc., Aeromatic-Fielder Division.)

and associates studied the flow of the wet mass as it is forced through a die [20,26,28,29]. They determined steady-state flow (described earlier; see Fig. 4) was essential to produce smooth extrudate that results in uniformly sized spherical particles having good sphericity and surface characteristics. Materials and processes that did not result in steady state, a condition referred to as forced flow, produced extrudate having surface impairments. In moderate cases, the surface is rough, while in more severe cases, a phenomenon commonly referred to as shark-skinning occurs. Examples of smooth extrudate and shark-skinned extrudate are shown in Fig. 10a and b, respectively.

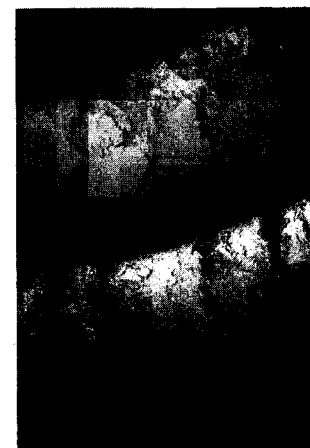
Force displacement profiles of microcrystalline cellulose (MCC) and water at various ratios, MCC, lactose, and water at a 5:5:6 ratio, and lactose and water at an 8:2 ratio, developed by Harrison et al., are shown in Fig. 11. Steady state was possible with the MCC and MCC-lactose samples, but not with lactose alone. As can be seen with the MCC samples, the duration of the compression stage was water level-dependent, with no effect seen on the steady-state stage. Additional studies indicated the effect of ram speed (extrusion speed) and die R/L ratio. An increase in ram speed increased the duration of the steady-state stage, with no effect on the compression stage. The R/L ratio had no effect on either compression or steady state. Wet mass composition, therefore, influenced the ability to achieve steady state, whereas the water level and ram speed influenced duration. Higher water levels decreased the force to produce steady-state flow, but increased the duration. Faster ram speeds (extrusion rates) increased the duration of steady state and increased the force. As discussed in the following, other investigators have reported the correlation between extrusion force and sphere quality.

Harrison et al. also indicated that a uniform lubricating layer at the die wall interface must occur to eliminate the slip-stick phenomenon responsible for forced flow. Development of a lubricating layer was dependent on the length of the die (a minimum length required), wall shear stress, and upstream pressure loss. They represent the frictional forces at the die wall interface and the estimated pressure loss at zero die length in the barrel of the ram extruder. The method for deriving these values has been determined [20]. These parameters permit a quantitative comparison between formulations and process; however, no specific values can be targeted because they vary with materials.

Pinto et al. also showed that, at slow ram speeds, water moves toward the die wall interface and acts as a lubricant, resulting in reduced extrusion forces. At higher speeds, water is unable to move rapidly through the mass, resulting in higher forces [30]. They indicated the water content and its distribution are critical in determining the particle size and sphericity of the product. A lower water content and higher speed will reduce the size and



(a)



(b)

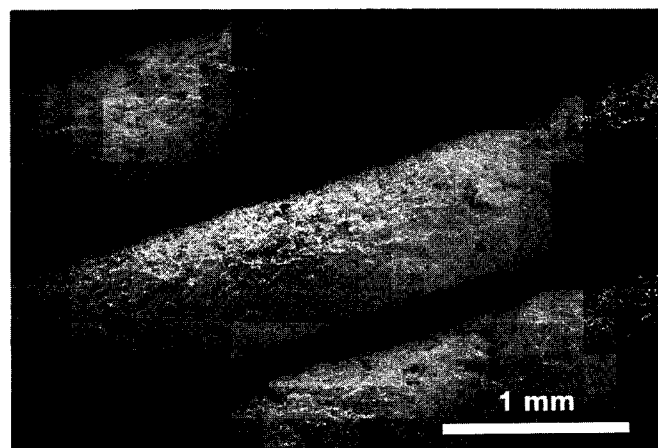
**Fig. 10** SEMs showing and having surface impairment, c

sphericity of the particles. adjusted to achieve the d the effect of die length u indicated the extrudate be of the die was increased [ enables the use of lower

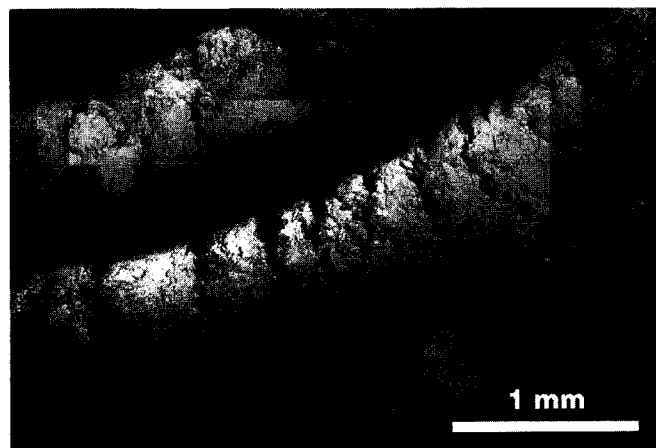
nas as it is forced through a die flow (described earlier; see Fig. 10a) that results in uniformly sized and surface characteristics. Ma- steady state, a condition referred g surface impairments. In mod- ore severe cases, a phenomenon curs. Examples of smooth extru- in Fig. 10a and b, respectively. crystalline cellulose (MCC) and water at a 5:5:6 ratio, and lactose Harrison et al., are shown in Fig. and MCC-lactose samples, but the MCC samples, the duration dependent, with no effect seen on indicated the effect of ram speed ease in ram speed increased the effect on the compression stage. ection or steady state. Wet mass ility to achieve steady state, uenced duration. Higher water dy-state flow, but increased the increased the duration of steady in the following, other investi- een extrusion force and sphere

form lubricating layer at the die p-stick phenomenon responsible ng layer was dependent on the red), wall shear stress, and up- rictional forces at the die wall zero die length in the barrel of ese values has been determined e comparison between formula- es can be targeted because they

am speeds, water moves toward t, resulting in reduced extrusion move rapidly through the mass, ated the water content and its article size and sphericity of the speed will reduce the size and



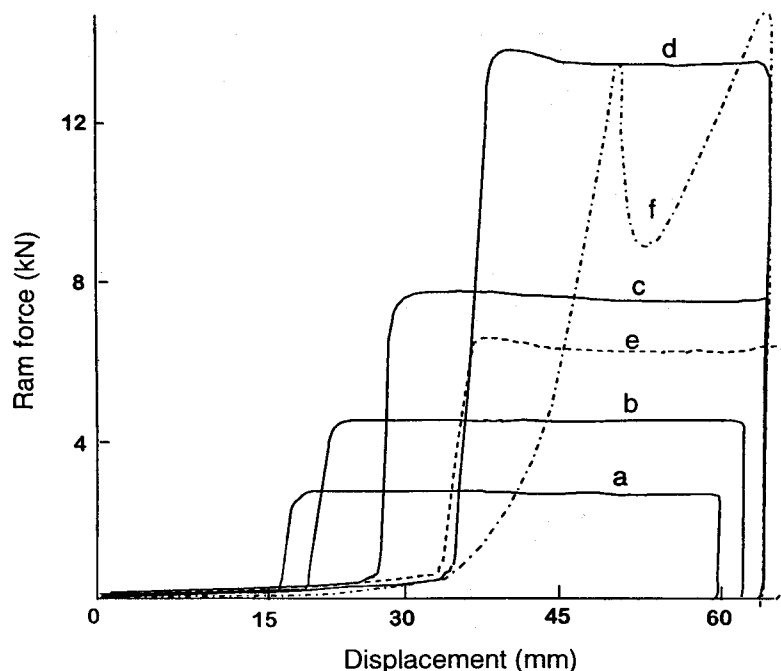
(a)



(b)

**Fig. 10** SEMs showing an example of (a) smooth extrudate and (b) extrudate having surface impairment, or shark-skinning.

sphericity of the particles. The extrusion speed and water content should be adjusted to achieve the desired effect. Other researchers have investigated the effect of die length using a gravity-feed radial extruder. Hellén et al. indicated the extrudate became smoother and more bound as the R/L ratio of the die was increased [31]. Vervae et al. reported that a higher R/L ratio enables the use of lower water levels to achieve a more bound extrudate



**Fig. 11** Force displacement profiles at various moisture contents of mixtures of microcrystalline cellulose and water: (a–d) microcrystalline cellulose–lactose–water (5:5:6); (e) lactose–water (8:2); (f) at a ram speed of  $4 \text{ mm s}^{-1}$ , die diameter of 1.0, and a length/radius ratio of 12. Percentage moisture content of microcrystalline cellulose–water mixtures: a, 59.4; b, 54.9; c, 51.1; d, 45.0. (From Ref. 20.)

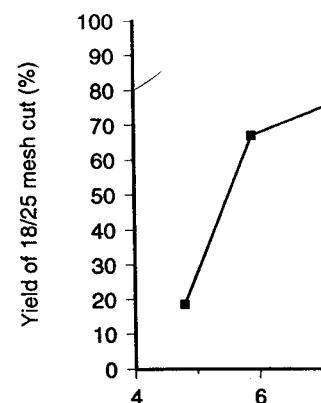
[32]. This also increased the range (drug loading and water level) over which quality spheres could be produced. They attributed the increased latitude and capability to increased densification, resulting in well-bound extrudate. The average pore diameter and bulk density reported for extrudate prepared from various MCC/DCP/water ratios at two R/L ratios are shown in Table 1. Baert et al. also indicated a similar increase in latitude when a cylinder extruder having a R/L ratio of 4 was compared with a twin-screw extruder having a R/L ratio of close to 1.8 [33]. There is an optimal pressure range over which extrudate capable of yielding acceptable spheres can be produced. Shah et al. demonstrated the correlation between screen pressure yield and density [34]. A high yield of spheres within a targeted narrow size distribution was produced as long as the screen pressure was maintained within a given range. The relation between yield and screen pressure is shown in Fig. 12.

**Table 1** Average Pore Diameter, Bulk Density, and Average Pore Volume of DCP–Avicel PH-101–Water Mixtures at Two R/L Ratios

Composition DCP–Avicel–water (w/w)	R/L Ratio
150:380:470	4
150:400:450	4
150:380:470	1.8
150:400:450	1.8

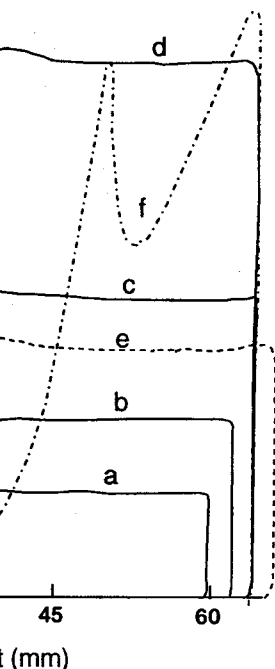
Source: Ref. 32.

Although many of the extrudates were cohesive extrudate, few had acceptable size distributions. Some researchers have reported that the use of a twin-screw extruder can produce extrudates with acceptable characteristics can be produced. O'Connor and Schwartz have reported that the use of a twin-screw extruder is advantageous in facilitating the spheronization step [35].



**Fig. 12** The effect of extrusion pressure on the yield of acceptable distribution. (From Ref. 35.)





us moisture contents of mixtures of microcrystalline cellulose-lactose-water of  $4 \text{ mm s}^{-1}$ , die diameter of 1.0, moisture content of microcrystalline 1.1; d, 45.0. (From Ref. 20.)

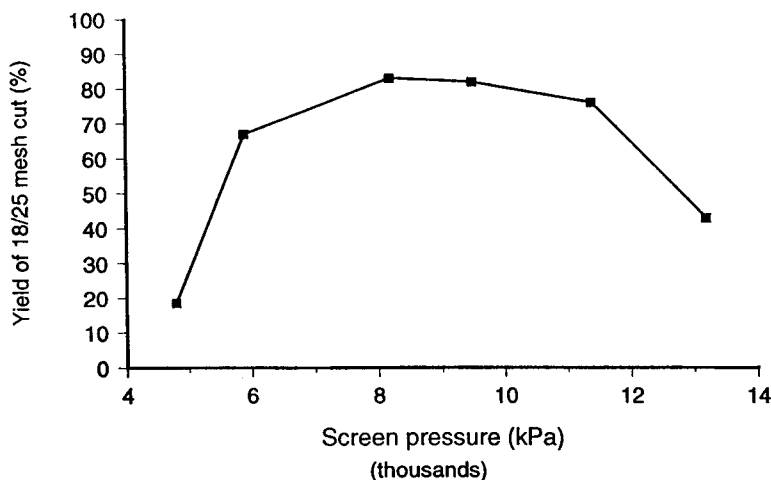
ding and water level) over which attributed the increased latitude and ing in well-bound extrudate. The reported for extrudate prepared from ratios are shown in Table 1. Baert latitude when a cylinder extruder a twin-screw extruder having a optimal pressure range over which eres can be produced. Shah et al. n pressure yield and density [34]. narrow size distribution was pro-maintained within a given range. sure is shown in Fig. 12.

**Table 1** Average Pore Diameter and Bulk Density of Extrudate Composed of DCP-Avicel PH-101-Water Mixtures, Extruded Using Screens with a Different R/L Ratio

Composition DCP-Avicel-water (w/w)	L/R ratio of screen	Average pore diameter ( $\mu\text{m}$ )	Bulk density (g/mL)
150:380:470	4	0.982	1.132
150:400:450	4	0.992	1.211
150:380:470	2	1.249	0.949
150:400:450	2	1.292	0.947

Source: Ref. 32.

Although many of the researchers have indicated a need for a more cohesive extrudate, few have expressed a need to remove all surface impairments. Some researchers have indicated that spheres having acceptable characteristics can be produced from extrudate having shark-skinning. O'Connor and Schwartz have found the presence of shark-skinning to be advantageous in facilitating the breakage of the extrudate during the spheronization step [35].



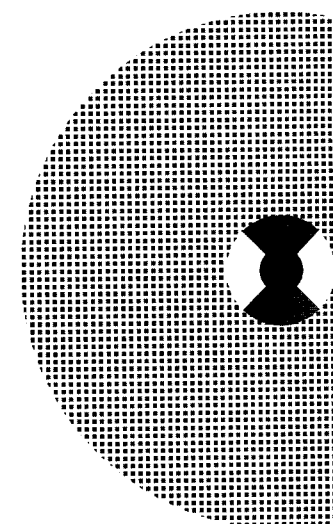
**Fig. 12** The effect of extruder screen pressure on the yield of particles within an acceptable distribution. (From Ref. 34.)

Experimental design studies conducted to concurrently investigate the effect of extrusion as well as other process and formulation variables have indicated that the extrusion variables are less important than granulating fluid level or variables of the spheronization step. Hasznos et al. determined that extruder speed had little effect on the size distribution of the final product or moisture change during processing, compared with the spheronization variables [36]. Hilemann et al. indicated that, when water/MCC ratios are held constant, a change in screen size results in a significant change in the size distribution [37]. However, in a study for which water level was included as a variable, Erkoboni et al. found [12] that the effect of screen size on size distribution is small compared with the effect of a change in water level. A change in water level can shift the mean size and still result in an acceptable distribution [12]. This is in agreement with earlier work by Malinowski and Smith, who also showed that the mean particle size is typically smaller than the size of the screen itself owing to shrinking during the drying step [4].

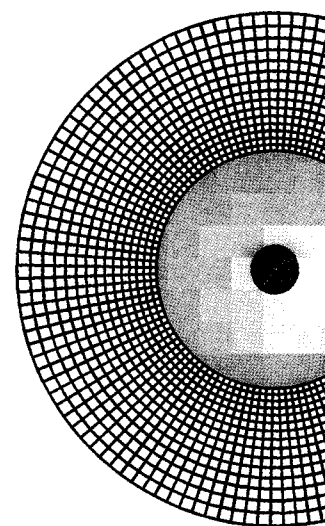
#### D. Spheronization

The fourth step in the extrusion-spheronization process is the spheronization step. It is carried out in a relatively simple piece of equipment. The working parts consist of a bowl having fixed sidewalls, with a rapidly rotating bottom plate or disk. The rounding of the extrudate into spheres is dependent on frictional forces. The forces are generated by particle-to-particle and particle-to-equipment interaction. Accordingly, the disk is generally machined to have a grooved surface, which increases the forces generated as particles move across its surface. Disks having two geometric patterns are produced, a cross-hatched pattern, with the grooves running at right angles to one another, and a radial pattern, with the grooves running radially from the center. The two varieties are shown graphically in Fig. 13. Some studies have shown the rate of spheronization to be faster with the radial pattern; however, both plates will result in an acceptable product [25].

During the spheronization step, extrudate is transformed from rod-shaped pellets into spherical particles. This transition occurs in various stages. Once charged into the spheronizer, the extrudate is drawn to the walls of the extruder by centrifugal forces. From here what happens is very much dependent on the properties of the extrudate. Under ideal conditions, the extrudate breaks into smaller, more uniform pieces. Within a short time period, the length of each piece is approximately equal to the diameter, owing to attrition and rapid movement of the bottom plate or disk. The differential in particle velocity as they move outward to the walls, begin to climb the walls, and fall back onto the rotating bed, along with the angular motion of the disk, results in a rope-like formation [3]. A graphic represen-



(a)



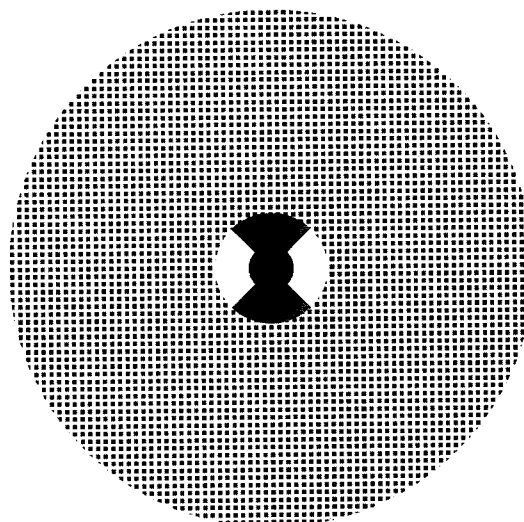
(b)

**Fig. 13** Spheronizer disks having a cross-hatched pattern with the grooves running at right angles to one another and a radial pattern with the grooves running radially from the center.

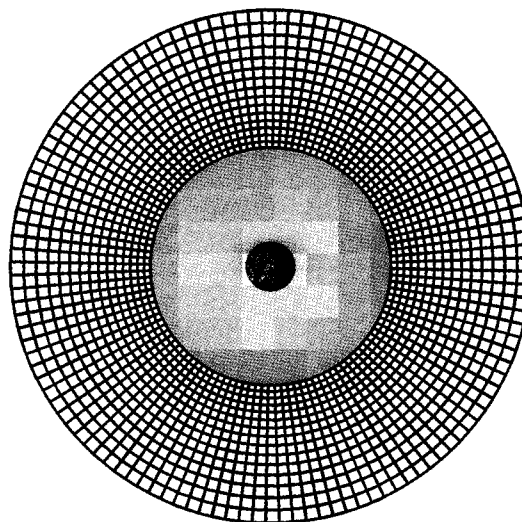
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e distribution of the final product  
ompared with the spheronization  
hat, when water/MCC ratios are  
ults in a significant change in the  
y for which water level was in-  
[12] that the effect of screen size  
h the effect of a change in water  
e mean size and still result in an  
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the mean particle size is typically  
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piece of equipment. The working  
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the forces generated as particles  
geometric patterns are produced,  
unning at right angles to one an-  
running radially from the center.  
Fig. 13. Some studies have shown  
the radial pattern; however, both  
[25].

rudate is transformed from rod-  
his transition occurs in various  
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ormation [3]. A graphic represen-



(a)

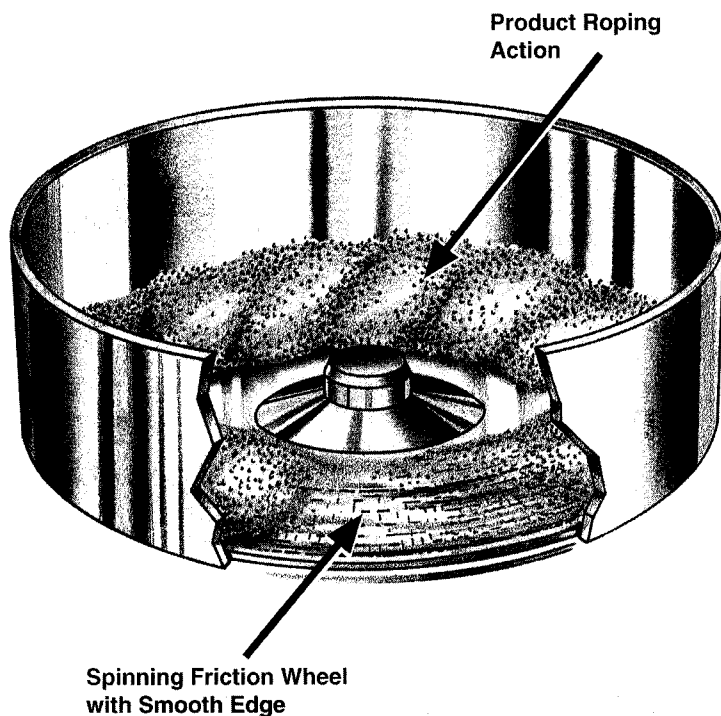


(b)

**Fig. 13** Spheronizer disks having two geometric patterns: (a) a cross-hatched pattern with the grooves running at right angles to one another and (b) a radial pattern with the grooves running radially from the center.

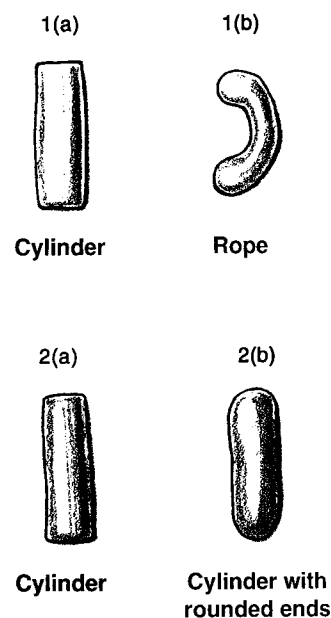
tation of this rope-like formation is shown in Fig. 14. This formation can be a critical indicator of the quality of the granulation or extrudate. As pointed out by Reynolds [3] the disk rotating without movement of the product indicates an overwet condition. The condition is caused either from a granulation that was initially overwet or migration of water or a fluid ingredient to the surface of the extrudate during extrusion or spheronization.

The transformation from cylinder-shaped extrudate to a sphere occurs in various stages. Two models have been proposed to describe the mechanism and are shown graphically in Fig. 15. The model proposed by Rowe [25] describes a transition whereby the cylindrical particles (see Fig. 15-2a) are first rounded off into cylindrical particles with rounded ends (see 15-2b), then form dumbbell-shaped particles (see 15-2c), ellipsoids (see 15-2d), and finally, spheres (see 15-2e). The second model proposed by Baert et al. [38] suggests that the initial cylindrical particles (see 15-1a) are deformed



**Fig. 14** A graphic representation of the characteristic rope like formation in a spheronizer bowl during operation.

## Extrusion-Spheronization f

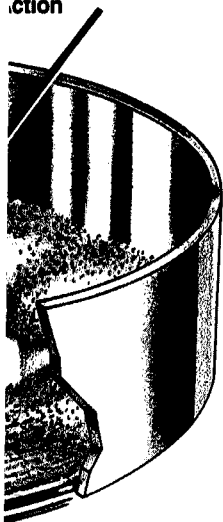


**Fig. 15** A graphic representation of the mechanism of spheronization. The model proposed by Rowe [25] describes a transition from cylindrical particles (2a) to rounded ends (2b), dumbbells (2c), ellipsoids (2d), and finally, spheres (2e). The second model proposed by Baert et al. [38] describes a transition from cylindrical particles (1a) to a rope (1b), a dumbbell (1c), two spherical particles (1d), and finally, spheres (1e). (From Refs. 25 and 38.)

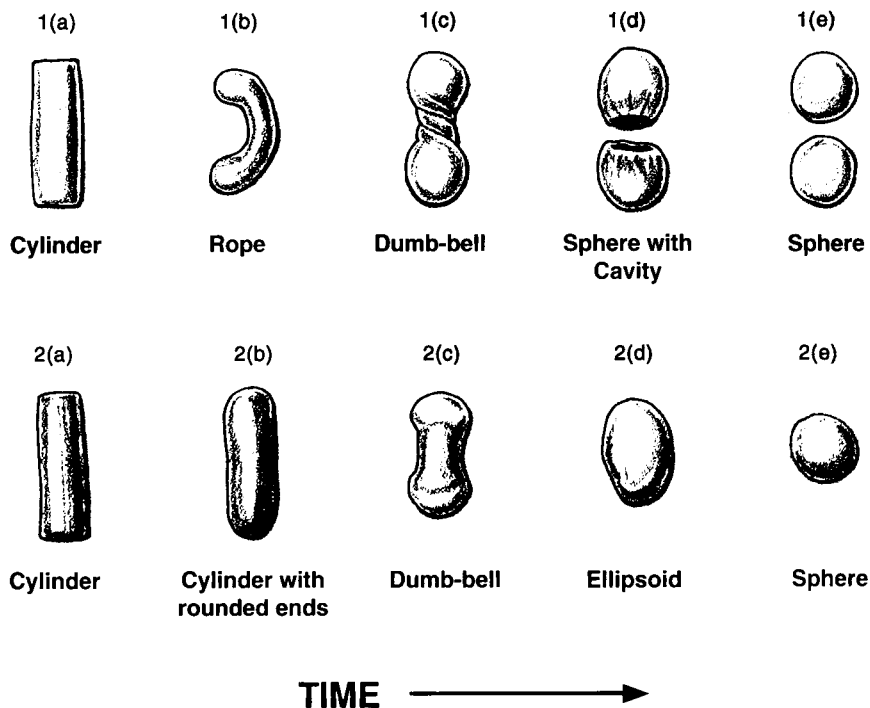
into a bent, rope-shaped particle with a twisted middle (see 15-1b). The rope then breaks into two spherical particles (see 15-1c). The process continues until the particles are round off into spheres (see 15-1e). The exact size distribution of the particles is revealed. The exact size distribution of the particles is revealed. If the extrudate is overwet, the particles will be too large. If the extrudate is underwet, the particles will be too small. The scanning electron micro

in Fig. 14. This formation can be granulation or extrudate. As long as there is no movement of the extrudate, the condition is caused either from migration of water or a fluid causing extrusion or spheronization. The extrudate to a sphere occurs when the extrudate is exposed to describe the mechanism. The model proposed by Rowe describes the transition of cylindrical particles (see Fig. 15-2a) to spheres with rounded edges (see 15-2b), ellipsoids (see 15-2c), ellipsoids (see 15-2d), and spheres (see 15-2e). The model proposed by Baert et al. describes the transition of cylindrical particles (see 15-1a) to spheres with rounded edges (see 15-1b), ellipsoids (see 15-1c), ellipsoids (see 15-1d), and spheres (see 15-1e).

Product Roping  
Action

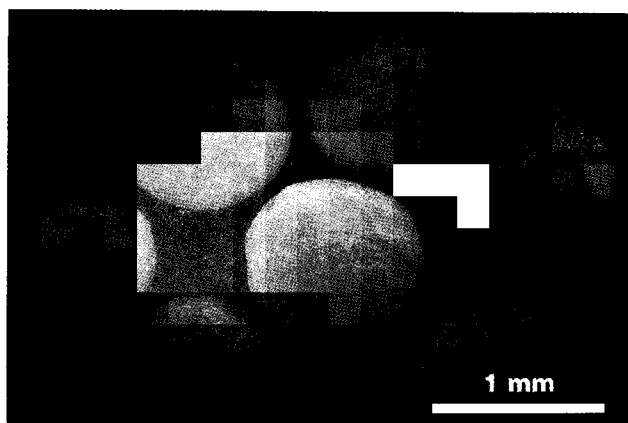


Characteristic rope like formation in a

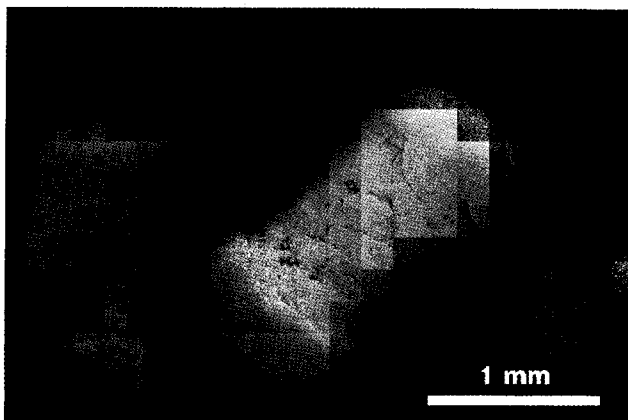


**Fig. 15** A graphic representation of the two models proposed to describe the mechanism of spheronization. The model proposed by Rowe [25] describes a transition from cylindrical particles (2a) into cylindrical particles with rounded ends (2b), dumbbells (2c), ellipsoids (2d), and spheres (2e). The model proposed by Baert et al. [38] describes a transition from initial cylindrical particles (1a) into a bent rope (1b), dumbbell (1c), two spherical particles with a hollow cavity (1d), and spheres (1e). (From Refs. 25 and 38.)

into a bent, rope-shaped particle (see 15-1b), then form a dumbbell with a twisted middle (see 15-1c). The twisting action eventually causes the dumbbell to break into two spherical particles, with a flat side having a hollow cavity (see 15-1d). Continued action in the spheronizer causes the particles to round off into spheres (see 15-1e). When the sphere is fractured a hollow particle is revealed. The exact mechanism is likely composition-dependent. If the extrudate is overwet, particle growth will occur, resulting in a broad size distribution. Underwet extrudate will not have enough plasticity to further round off in the spheronizer; the result is the formation of dumbbells. The scanning electron micrographs (SEMs) in Fig. 16 show an example of



(a)



(b)

**Fig. 16** An example of (a) good spheres produced from a sufficiently plastic mass and (b) dumbbells that would not deform further produced from underwet extrudate.

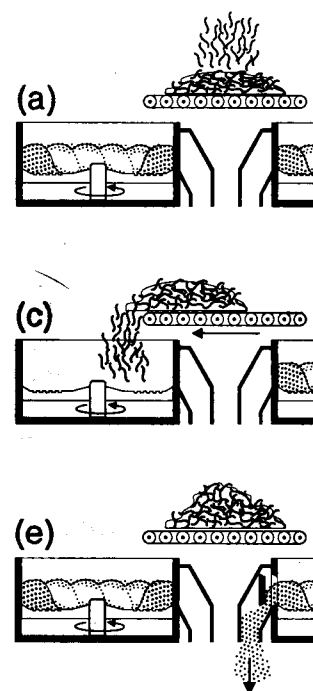
good spheres produced from a sufficiently plastic mass and dumbbells that would not deform further.

Of the two process steps unique to extrusion-spheronization, the first, extrusion, is a continuous process, whereas the second, spheronization, is a batch process. To make the process viable for commercial operations, two systems have been developed to enable the extruder to continuously feed material to the spheronizer(s). The first system is a semicontinuous shuttle system, and the second is a cascade system. The shuttle system is typically

## Extrusion-Spheronization

used when uniform particle coating applications. The extrusion-spheronization process is used in applications in which less size uniformity is required, and extrusions intended for compaction.

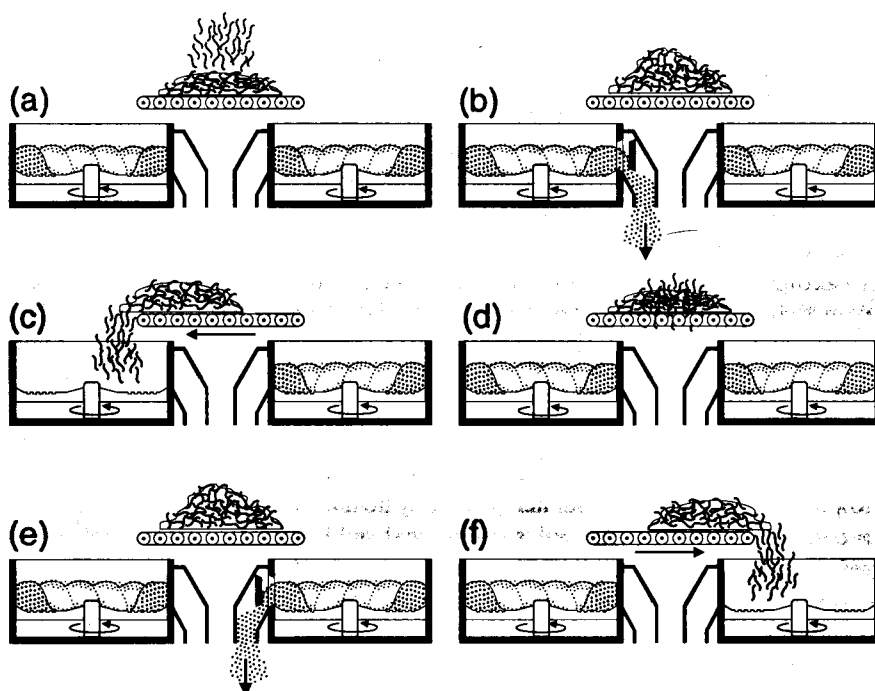
The shuttle system uses two spheronizers to fill one spheronizer while the other is empty to collect extrudate in a shuttle receptacle. The cycle is operational, and fill the second spheronizer at the end of its cycle. The shuttle system is shown in Fig. 18. A picture of a Caleva spheronizer is shown in Fig. 18. The case of the shuttle system are modified to have the diameter of the extruder. This results in a spheronizer



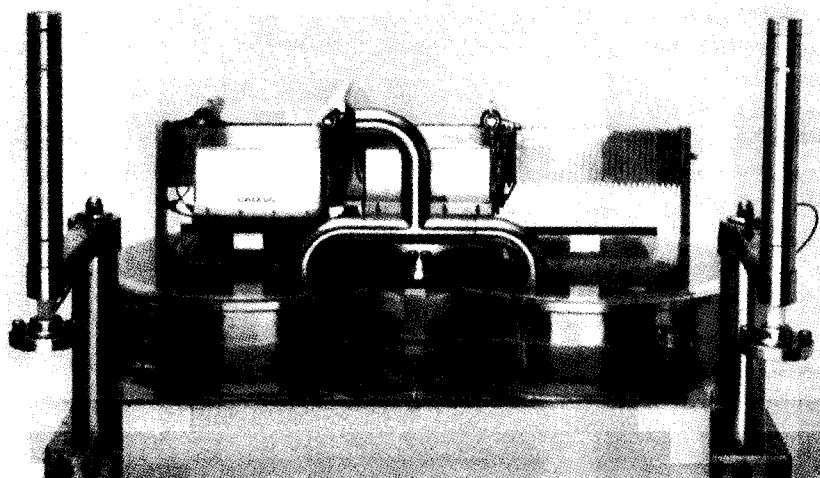
**Fig. 17** A graphic representation of the shuttle system for extrusion-spheronization. (a) The extruder feeds material into the first spheronizer. (b) The first spheronizer fills while the second is empty. (c) The first spheronizer empties into a shuttle receptacle. (d-f) The cycle repeats itself.

used when uniform particles are required, such as for controlled-release-coating applications. The cascade system, however, can be used for applications in which less size and shape uniformity is required, such as granulations intended for compression.

The shuttle system uses two spheronizers in parallel. It is designed to fill one spheronizer while the second is in the middle of its cycle, continue to collect extrudate in a shuttle receptacle while they are both full and operational, and fill the second after it empties and the first unit is in the middle of its cycle. The shuttle system operation is shown graphically in Fig. 17. A picture of a Caleva spheronizing system having twin spheronizers is also shown in Fig. 18. The cascade operation uses one or more spheronizers that are modified to have the disks some distance below the discharge chute [27]. This results in a spheronization zone having a fixed volume. The product is



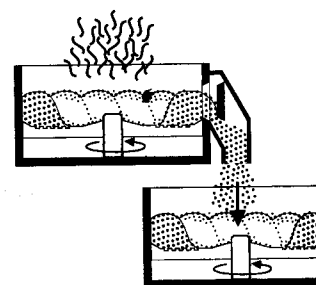
**Fig. 17** A graphic representation of a twin spheronizer shuttle system using two spheronizers in parallel and a shuttle receptacle: (a) When both units are full the shuttle receptacle collects extrudate. (b) After one empties, (c) the shuttle box fills it. (d-f) The cycle repeats itself for the second unit. (From Ref. 27.)



**Fig. 18** A Caleva spheronizing system having twin spheronizers and a shuttle receptacle. (Courtesy of GEI Processing Inc.)

continually fed from either the extruder or a previous spheronizer. As the charge volume grows from incoming material some product is discharged. The residence time is dictated by the feed rate. The reduced size and shape distribution are due to the percentage of material that does not reside in the spheronization zone for the intended time. The number of spheronizers placed in sequence depends on the desired outcome. However, if only a slight rounding with minimal densification is required, one spheronizer with a short residence time will be sufficient. The cascade operation is shown graphically in Fig. 19.

Variables in the spheronization step include spheronizer size, charge, disk speed, and residence time. Each one of the variables has the potential to play a major role in influencing the physical characteristics of the resulting product. Hasznos et al. [36] showed that a higher disk speed and longer residence time increased the coarse fraction and mean diameter and decreased the fine fraction. The faster speed and longer time also increased the moisture loss during the process. Because the moisture loss can reduce the plasticity of the particle, it can have the same effect as an underwet granulation. The particles may not round off into spheres and may stay as deformed cylinders or dumbbells. Higher spheronizer charges reduced the moisture loss. They also suggested that an interaction between spheronizer speed and residence time indicated the total number of revolutions of the disk was critical. A change in one of the variables could be offset by an



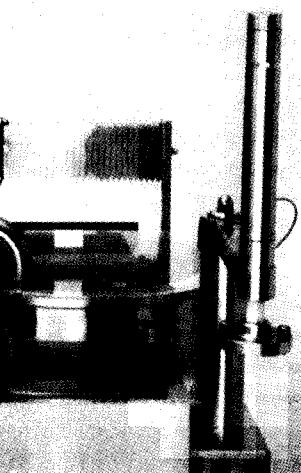
**Fig. 19** A graphic representation of a cascade system. Product is continually fed into the first spheronizer and is discharged. (From Ref. 27.)

opposite change of the other variables. However, the density remained constant [36]. He also discussed the effect of spheronization [17]. In addition to increasing the shape of the spheronized product. High speed and long time processing indicated that a minimum residence time around the cylinder-shaped disk was required, or time, up to a limit, increased the density. Higher speeds and longer times at high disk speeds resulted in a more spherical product.

Several investigators have studied the effect of residence time on density. Work has shown that they have no effect on the density of the granulation and extrusion process in other studies; however, the effect is dependent on formulation. The oil can reduce the density during extrusion and between particles. A number of investigators have shown that an increase in either disk speed or residence time increased density [11,12,17,37].

O'Connor et al. indicated that the density increased with increasing residence time and decreased [15]. Erko-boni et al. showed that the result was reduced friability

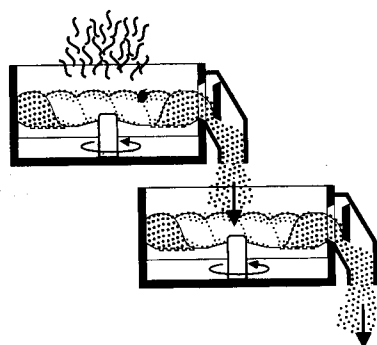




twin spheronizers and a shuttle re-

a previous spheronizer. As the material some product is discharged. The reduced size and shape of material that does not reside in the spheronizer. The number of spheronizers required and outcome. However, if only a single spheronizer is required, one spheronizer with a cascade operation is shown

include spheronizer size, charge, and the number of revolutions. If the variables has the potential to influence the characteristics of the resulting granulation, a higher disk speed and longer residence time and mean diameter and density. A longer time also increased the moisture loss can reduce the same effect as an underwet extrudate. The off into spheres and may stay as irregular spheres. Spheronizer charges reduced the interaction between spheronizer charges. A small number of revolutions of the extruder could be offset by an



**Fig. 19** A graphic representation of two spheronizers in sequence to form a cascade system. Product is continually fed and, as the charge volume grows, product is discharged. (From Ref. 27.)

opposite change of the other, as long as the total number of revolutions remained constant [36]. Hellén et al. showed a similar moisture loss during spheronization [17]. In addition they indicated that the major factors influencing the shape of the spheres were the disk speed and residence time. High speed and long time produced more spherical particles [17]. Wan et al. indicated that a minimum disk speed and residence time were required to round the cylinder-shaped extrudate [39]. Furthermore, an increase in speed or time, up to a limit, increased the median diameter of the spheres, whereas higher speeds and longer times caused a reduction in size. Short residence times at high disk speeds resulted in small, but round particles [39].

Several investigators have reported the effect of disk speed and residence time on density. Woodruff and Neussle reported that the variables have no effect on the density of the spheres, when compared with the density of the granulation and extrudate [7]. These results conflict with most of the other studies; however, they are likely due to the use of mineral oil in the formulation. The oil can reduce the frictional forces at the die wall during extrusion and between particles and equipment surfaces during spheronization. A number of investigators including Malinowski and Smith reported an increase in either disk speed or residence time resulted in an increase in density [11,12,17,37].

O'Connor et al. indicated that the friability of placebo spheres decreased with increasing residence time, whereas the mean particle diameter decreased [15]. Erko-boni et al. showed an increase in extruder screen size resulted in reduced friability [12].

## E. Drying

Drying is the final step in the process. This can be accomplished in any dryer that can be used for conventional-type granulations, including tray dryers, column-type fluid beds, and deck-type vibratory fluid beds. Each of the drying techniques has advantages; however, the major differences are based on the rate of water removal. Tray drying is the slowest of the processes. Fluidized bed dryers result in a much more rapid drying rate because of the higher air volumes and the potential use of higher inlet temperatures. Column fluid beds are batch dryers, whereas the deck-type dryers offer the advantage of a continuous process. Both have been used successfully in drying product produced by extrusion-spheronization. The drying process must be chosen based on the desired particle properties.

Tray drying is a slow process in a static bed. Because of this, it can offer the greatest opportunity for a drug to migrate toward the surface and recrystallize [40]. The more rapid rate in a fluid bed will likely minimize the effects of migration. This phenomenon can have an effect on several particle properties. The increased active concentration at the surface of the particle can increase the rate of dissolution. This recrystallization, however, can cause a problem for applications requiring film coating because the smooth surfaces developed by the spheronization process would be damaged. Additionally, the crushing strength of tray-dried particles will likely be greater than their fluid bed counterparts. The slow recrystallization in the static bed allows crystal bridges to develop as the fluid is removed and the solute recrystallizes.

## IV. FORMULATION VARIABLES

The composition of the wet mass is critical in determining the properties of the particles produced. This is clearly understood if we look at what material behaviors are required during each of the process steps. During the granulation step, a plastic mass is produced—a simple enough task if ended there. The materials must form a plastic mass, deform when extruded, and break off to form uniformly sized cylindrical particles. A minimal amount of granulating fluid should migrate to the surface during extrusion, and the particles should stay discrete during collection. During spheronization the particles must round off to form uniformly sized spheres. They must not dry out because of temperature or air volume, or grow in size by agglomeration. The fact is, a lot is asked from materials used in this process. This is especially true of formulations containing high percentages of the active agent

when low levels of excipient are present in the mass.

The importance of using water as the granulating fluid has been discussed on. Conine and Hadley cited the importance of water [2]. Reynolds went on to indicate the importance of type binders [3]. He cited cellulose derivatives as adhesives, and recommended capillary-type binders. Since the importance of an attempt to understand the science of granulation studies are discussed in the literature.

O'Connor et al. studied the effect of water on extrusion-spheronization. They found that using water as the granulating fluid was important in the process. Of the binders, Na-CMC was capable of being used with phosphate, lactose, starch, and many other materials.

In an additional study, O'Connor et al. studied the effect of excipient, and excipient/drug ratio on the spheronizing excipient played the role of the properties. For low-dose applications, they found the best excipient to use was Na-CMC. For moderate drug loading (50% drug), MCC coprocessed with Na-CMC resulted in acceptable spheres. MCC did not yield acceptable spheres. MCC spheres produced using Avicel PH 102 did not yield acceptable spheres. They found dissolution to be a function of solubility, and concentration of the drug. MCC remained intact and broke down into particles containing the coprocessed drug. The spheres in a basket and were described as having release profiles for spheres containing 50:50 ratio are shown in Fig. 22. The spheres containing different drug loads showed that a high load resulted in an increased release rate. The spheres containing active agents having a high release rate, like maleate, quinidine sulfate, and others, are shown in Fig. 22. An increase in the release rate [41].

Millili and Schwartz discussed the effect of water and ethanol at various ratios on the release rate. The release rate changed significantly as the

this can be accomplished in any type granulations, including tray type vibratory fluid beds. Each of however, the major differences are drying is the slowest of the pro- h more rapid drying rate because use of higher inlet temperatures. as the deck-type dryers offer the have been used successfully in neronization. The drying process le properties.

tatic bed. Because of this, it can o migrate toward the surface and a fluid bed will likely minimize n can have an effect on several ncentration at the surface of the . This recrystallization, however, quiring film coating because the nization process would be dam- of tray-dried particles will likely . The slow recrystallization in the p as the fluid is removed and the

l in determining the properties of rstood if we look at what material process steps. During the granu- mple enough task if ended there. eform when extruded, and break icles. A minimal amount of gran- during extrusion, and the particles ring spheronization the particles spheres. They must not dry out grow in size by agglomeration. used in this process. This is es- gh percentages of the active agent

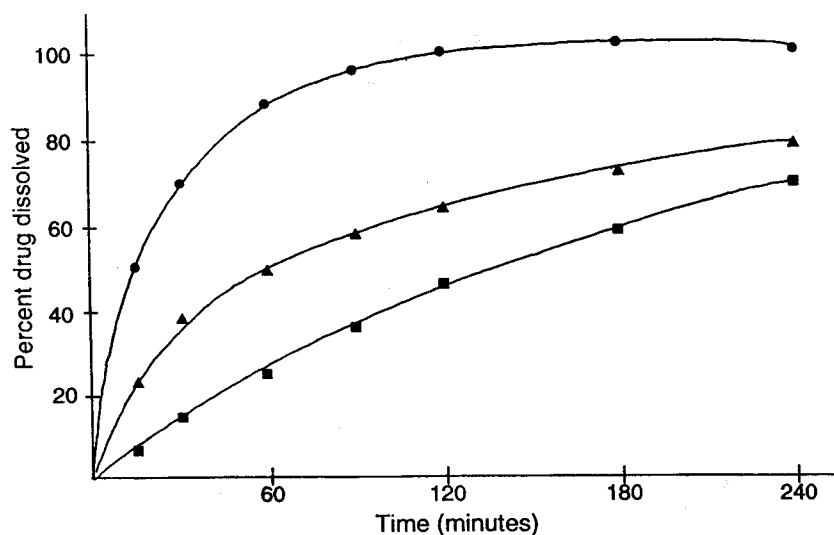
when low levels of excipients are used to impart the desired properties to the mass.

The importance of using sphere-forming excipients was noted early on. Conine and Hadley cited the necessity of using microcrystalline cellulose [2]. Reynolds went on to indicate the need for either adhesive or capillary-type binders [3]. He cited cellulose gums, natural gums, and synthetic polymers as adhesives, and microcrystalline cellulose, talc, and kaolin as capillary-type binders. Since then, much work has been conducted in an attempt to understand the significance of material properties. Some of the studies are discussed in the following.

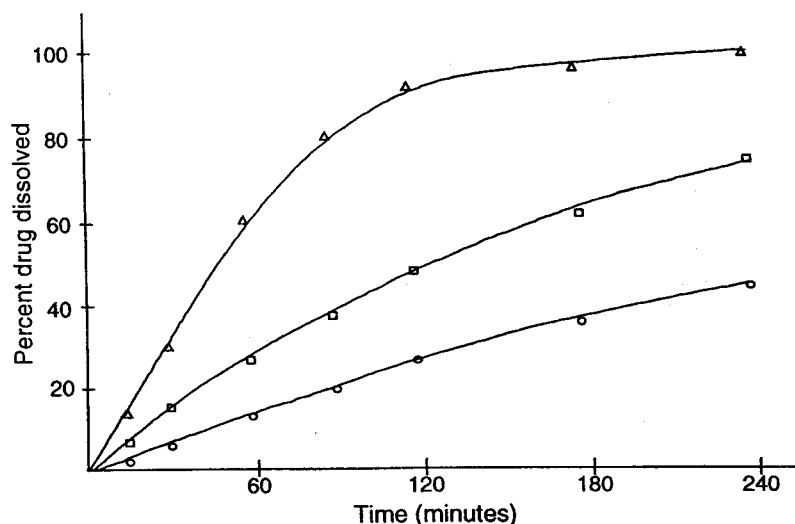
O'Connor et al. studied the behavior of some common excipients in extrusion-spheronization. The materials were studied as single components using water as the granulating fluid in an attempt to understand their application in the process. Of the materials tested, only the MCC or MCC with Na-CMC was capable of being processed. Others, including dicalcium phosphate, lactose, starch, and modified starch, did not process adequately [15].

In an additional study, they investigated the effect of varying drug, excipient, and excipient/drug ratios. At low drug levels they found the spheronizing excipient played the most significant role in determining sphere properties. For low-dose applications, microcrystalline cellulose (MCC) was the best excipient to use because it formed the most spherical particles. At moderate drug loading (50%), MCC as well as the two products consisting of MCC coprocessed with Na-CMC (Avicel RC-581 and Avicel CL-611) resulted in acceptable spheres. At higher-loading levels, however, the MCC did not yield acceptable spheres, and the coprocessed materials did. The spheres produced using Avicel CL-611 were the most spherical. In addition, they found dissolution to be dependent on the type of excipient used, the solubility, and concentration of the active component. Spheres containing MCC remained intact and behaved as an inert matrix system, whereas those containing the coprocessed products formed a gel plug in the dissolution basket and were described as water-swallowable, hydrogel matrix systems. The release profiles for spheres containing each of the excipients and theophylline in a 50:50 ratio are shown in Fig. 20. Release profiles for spheres containing different drug loads are shown in Fig. 21. An increase in drug load resulted in an increased release rate. Release profiles for spheres containing active agents having different solubilities, including chlorpheniramine maleate, quinidine sulfate, theophylline, and hydrochlorothiazide are shown in Fig. 22. An increase in drug solubility resulted in an increased release rate [41].

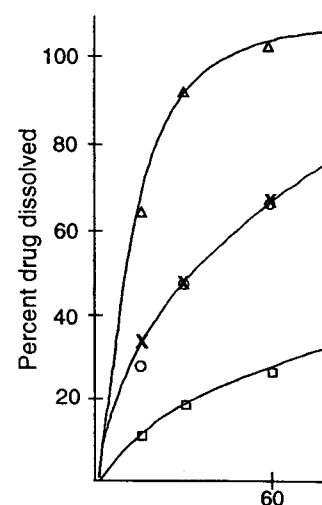
Millili and Schwartz demonstrated the effect of granulating with water and ethanol at various ratios [9]. The physical properties of the spheres changed significantly as the ratio of the two fluids was varied. Spheres could



**Fig. 20** Dissolution profiles of spheres containing 50% theophylline in different Avicel MCC types: ●, Avicel PH-101; ▲, Avicel RC-581; ■, Avicel CL-611. (From Ref. 41.)



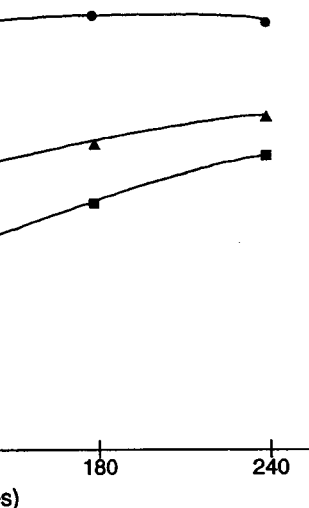
**Fig. 21** Dissolution profiles of spheres containing different concentrations of drug in Avicel CL-611: ○, 10%; □, 50%; △, 80%. (From Ref. 41.)



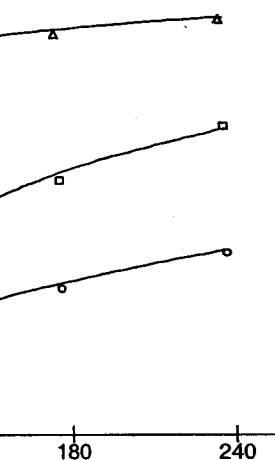
**Fig. 22** Dissolution profiles of chlorpheniramine maleate; ○, zide. (From Ref. 41.)

not be formed with absolute ethanol. An increase in the friability, dissolution, and compressibility of spheres granulated with water-granulated product has been observed. When water-granulated product was used, spheres remained intact. As previously discussed, water-granulated product is more compressible than those prepared by dry granulation. The proposed bonding mechanism is shown in Figure 1. The differences in the properties of the two products. *Autohesion* is a term used to describe the interdiffusion of free polymer chains [42].

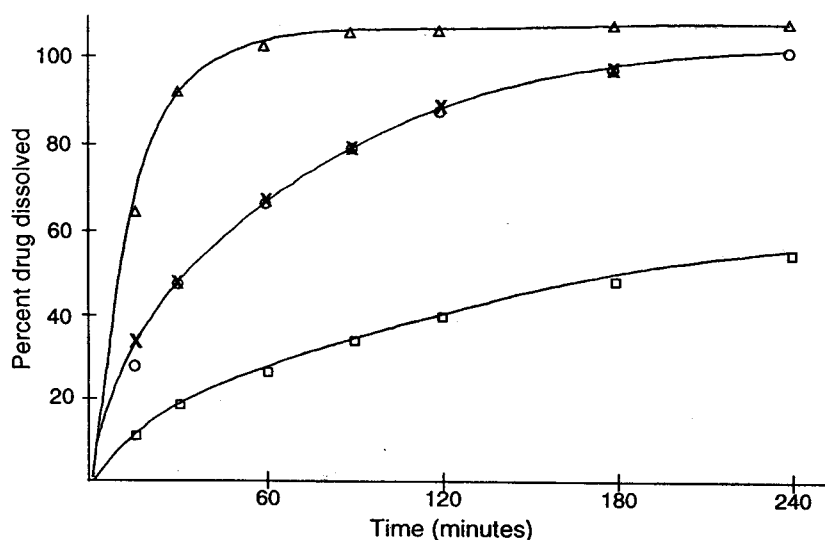
By using a ram extruder, the flow could not be achieved. The results demonstrated the reduced sensitivity of the system determined by the force required to compress the MCC comparing MCC with a MC



ing 50% theophylline in different  
RC-581; ■, Avicel CL-611. (From



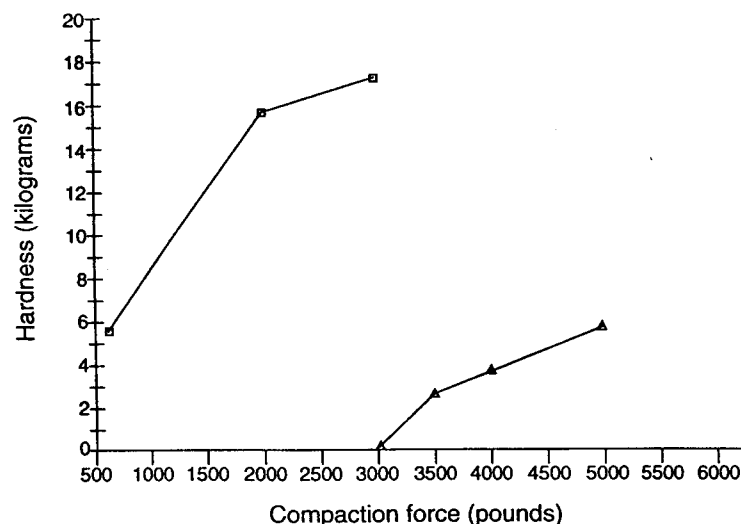
ing different concentrations of drug  
om Ref. 41.)



**Fig. 22** Dissolution profiles of spheres containing 10% drug in Avicel PH-101: Δ, chlorpheniramine maleate; ○, quinidine sulfate; X, theophylline; □, hydrochlorothiazide. (From Ref. 41.)

not be formed with absolute ethanol, but were possible with 5:95 water-ethanol. An increase in the water fraction resulted in a decrease in porosity, friability, dissolution, and compressibility, and an increase in density. The porosity of spheres granulated with 95% ethanol was 54%, whereas the water-granulated product had a porosity of 14%. When more than 30% water was used, spheres remained intact throughout the dissolution test. As previously discussed, water-granulated spheres were very difficult to compress, whereas spheres granulated with 95% ethanol were significantly more compressible than those prepared using water [9]. A tablet hardness versus compression forces profile is shown in Fig. 23. In a later study [42], Millili et al. proposed a bonding mechanism, referred to as *autohesion*, to explain the differences in the properties of spheres granulated with water and ethanol. *Autohesion* is a term used to describe the strong bonds formed by the interdiffusion of free polymer chain ends across particle-particle interfaces [42].

By using a ram extruder, Harrison et al. demonstrated that steady-state flow could not be achieved with lactose [20]. Additionally, they demonstrated the reduced sensitivity of MCC to small changes in moisture, as determined by the force required to induce plug flow in a cylinder. When comparing MCC with a MCC-lactose blend and 100% lactose, they found

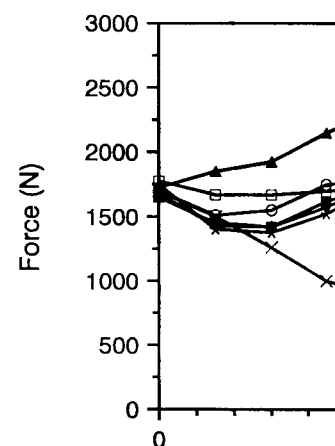


**Fig. 23** The effect of varying compression force on the hardness of compacted 16/30-mesh spheres of 10% theophylline-Avicel PH-101:  $\Delta$ , spheres prepared by water;  $\square$ , spheres prepared by 95% ethanol granulation. (From Ref. 9.)

that, with lactose, small changes in moisture caused large changes in force, whereas with MCC, larger changes in moisture were required to have similar effects on the force [20].

Baert et al. used mixtures of microcrystalline cellulose and coexcipients at various ratios to demonstrate the effect of solubility and the total fluid on extrusion forces [23]. They showed that if the coexcipient was insoluble, such as dicalcium phosphate, the force required to extrude increased with increasing levels of coexcipient. When a soluble excipient, such as lactose, was used, the force required to extrude decreased with the addition of the initial amounts of lactose. After a certain level, however, the reduction in force stopped and began to increase. This was due to the initial solubilization of lactose and the resulting increase in the total fluid level. Once the fluid was saturated, the remaining lactose became insoluble, and the force began to increase. The increase began at about a 10% lactose level for  $\alpha$ -lactose and 20% for  $\beta$ -lactose. This was due to the difference in solubility between the two materials [23]. The effects of dicalcium phosphate and various lactose grades on extrusion force are shown in Fig. 24.

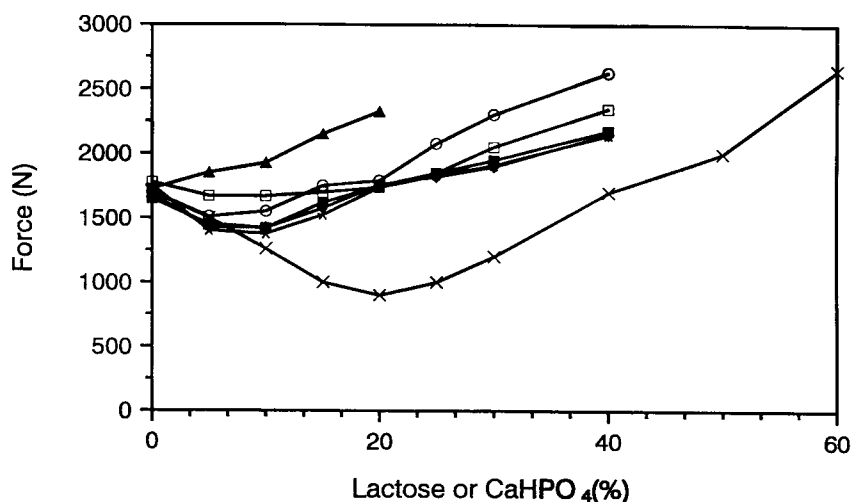
Schwartz et al. demonstrated that the compaction characteristics of MCC processed into spheres are significantly different from those of the original powder [8]. The powder material forms hard compacts at low com-



**Fig. 24** Influence of the amount of lactose (total weight) on the extrusion force for dicalcium phosphate dihydrate-Avicel PH 101. Each point is the mean of six values.  $\circ$ , monohydrate 200 mesh;  $\square$ ,  $\alpha$ -lactose;  $\triangle$ , DCL 11;  $\blacksquare$ , anhydrous  $\beta$ -lactose;  $\times$ , type of dicalcium phosphate dihydrate.

pression forces, whereas the powder material forms hard compacts, even at high force. MCC showed a high degree of compaction over a wide range. Inclusion of coexcipients increased the compactability but the pressure range over which the spheres formed was seen with dicalcium phosphate; however, the compaction profiles of spheres of MCC, MCC-DCP, or MCC-DCP-lactose were similar [25]. A similar phenomenon was observed for spheres produced by rotor granulation.

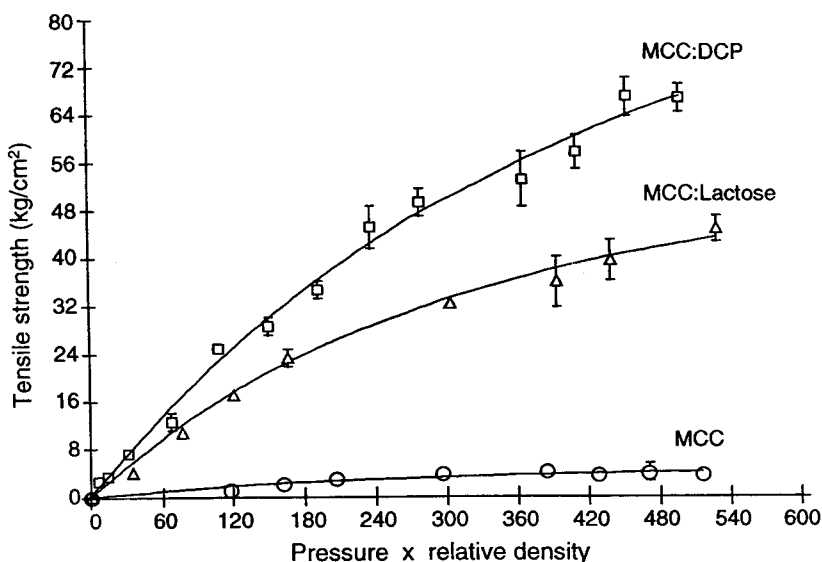
Funck et al. showed that the use of MCC was necessary to produce high drug-loaded spheres. Materials such as carbomer, hydroxypropylcellulose (HPC),



**Fig. 24** Influence of the amount of lactose or dicalcium phosphate dihydrate (% total weight) on the extrusion forces (N) for mixtures of lactose or dicalcium phosphate dihydrate-Avicel PH 101-water after granulation with a planetary mixer. Each point is the mean of six values. The SD is lower than 3% for each point. Six different types of lactose were used:  $\alpha$ -lactose monohydrate 80 mesh,  $\square$ ;  $\alpha$ -lactose monohydrate 200 mesh,  $\circ$ ;  $\alpha$ -lactose monohydrate 325 mesh,  $\diamond$ ; spray-dried lactose DCL 11,  $\blacksquare$ ; anhydrous  $\beta$ -lactose DCL 21,  $\times$ ; anhydrous  $\alpha$ -lactose DCL 30,  $*$ ; one type of dicalcium phosphate dihydrate was used,  $\blacktriangle$ . (From Ref. 23.)

pression forces, whereas the spheres are not compressible and form soft compacts, even at high forces. They indicated that spheres prepared from MCC showed a high degree of viscoelasticity over the entire compression range. Inclusion of coexcipients, such as lactose and dicalcium phosphate, increase the compactability by decreasing the viscoelastic resistance or pressure range over which the spheres behave elastically. A reduction in viscoelastic resistance was seen with spheres containing both lactose and dicalcium phosphate; however, dicalcium phosphate had a greater effect. Compaction profiles of spheres containing 10% theophylline with either MCC, MCC-DCP, or MCC-lactose in a 22.5:67.5 ratio are shown in Fig. 25. A similar phenomenon was reported by Maganti and Celik when pellets produced by rotor granulation were compressed [43].

Funck et al. showed that low levels of common binders could be used to produce high drug-loaded spheres with microcrystalline cellulose [44]. Materials such as carbomer, sodium carboxymethylcellulose (Na-CMC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), povi-



**Fig. 25** The effect of excipients on the compaction profile of spheres: Compaction profiles of spheres containing 10% theophylline with either MCC, MCC-DCP, or MCC-lactose in a 22.5:67.5 ratio using the Leuenberger model. (From Ref. 8.)

done (PVP), and pregelatinized starch were used. All materials were capable of producing spheres of acceptable quality. Dissolution testing showed that spheres containing HPC and HPMC remained intact during testing, whereas those containing starch, PVP, and Na-CMC disintegrated [44].

Lender and Kleinbudde reported that spheres produced with powdered cellulose had higher porosity and faster dissolution than those made using microcrystalline cellulose [45]. Spheres could not be produced using only powdered cellulose and drug; a binder was required. The higher porosity of the spheres prepared from powdered cellulose may be beneficial for applications requiring compression [45].

Feilden et al. [46] showed that increasing the particle size of lactose resulted in forced flow and high extrusion forces, which resulted in poor quality extrudate and spheres having a wide size distribution. This was attributed to the increased pore diameter of the mixture containing the coarse lactose, which allowed greater movement of water.

Chien and Nuesle [47] showed the use of a surfactant, such as sodium lauryl sulfate, reduced the migration of drug to the surface of the sphere during drying by reducing the surface tension of the granulating fluid. The

reduction in surface tension of the granulating fluid resulted in a smoother extrudate in some cases.

Some miscellaneous observations have been reported that excess extrudate, more MCC, binder, or water was required that sphere hardness was more variable, and the level of granulation was lower. It was noted that MCC had a narrower weight distribution than MCC coprocesses. The surface characteristics were different, giving smoother surfaces.

## VI. SUMMARY

Extrusion-spheronization is a process for producing tablets or spheres having unique properties. It is a labor- and time-intensive process that should be considered as a granulation process. It cannot be produced with microcrystalline cellulose alone. There are many conditions, including binder, granulation, and compression. Regardless of the application, the desired properties and the process must be achieved. Lastly, the process development and process development are high degree of interactions between the process and the product.

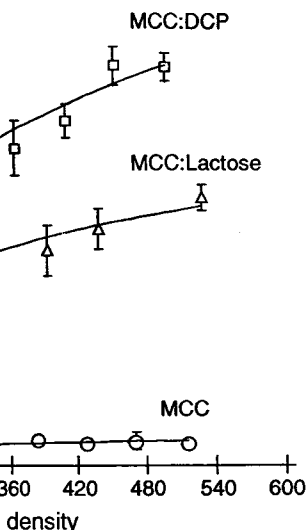
## ACKNOWLEDGMENTS

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## REFERENCES

1. Nakahara. US Patent 3,271,000.
2. JW Conine, HR Hadley. *Drug Cosm Ind* 106:38-40 (1984).
3. AD Reynolds. A new technique for the production of microspheres. *Chem Aerosol News* 41:40 (1984).





Compaction profile of spheres: Compaction with either MCC, MCC-DCP, or Lactose. (From Ref. 8.)

used. All materials were capable of being compressed. Dissolution testing showed that the spheres remained intact during testing, whereas the control disintegrated [44].

The spheres produced with powdered MCC showed better dissolution than those made using lactose. The higher porosity of the spheres may be beneficial for application.

Increasing the particle size of lactose and the forces, which resulted in poor particle size distribution. This was attributed to the mixture containing the coarse particles of water.

The use of a surfactant, such as sodium lauryl sulfate, to the surface of the sphere during the granulating fluid. The

reduction in surface tension also made it difficult to produce a cohesive extrudate in some cases.

Some miscellaneous observations include the following. Reynolds reported that excess extrudate friability can be overcome by incorporating more MCC, binder, or water in the granulation [3]. Erkoboni et al. indicated that sphere hardness was most affected by the level of MCC in the formulation and the level of granulating fluid used [12]. Hileman et al. showed that MCC had a narrower water range over which quality spheres could be made than MCC coprocessed Na-CMC [37]. Hellén et al. showed that the surface characteristics were influenced by the water level, with higher water levels giving smoother surfaces [17].

## VI. SUMMARY

Extrusion-spheronization is a versatile process capable of producing granules or spheres having unique physical properties. Because it may be more labor- and time-intensive than the more common granulation techniques, it should be considered as a granulating technique when the desired properties cannot be produced with more conventional techniques. Potential applications are many, including both immediate- and controlled-release drug dosages. Regardless of the application, care must be taken to understand the desired properties and the formulation and process variables capable of achieving them. Lastly, the use of statistical experimental design for formulation and process development is strongly recommended owing to the high degree of interactions between the variables.

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## REFERENCES

1. Nakahara. US Patent 3,277,520. October 1966.
2. JW Conine, HR Hadley. Preparation of small solid pharmaceutical spheres. *Drug Cosm Ind* 106:38-41, 1970.
3. AD Reynolds. A new technique for the production of spherical particles. *Manuf Chem Aerosol News* 41:40-43, 1970.

4. IM Jalal, HJ Malinowski, WE Smith. Tablet granulations composed of spherical-shaped particles. *J Pharm Sci* 61:1466–1468, 1972.
5. GM Clarke, JM Newton, MB Short. Comparative gastrointestinal transit of pellet systems of varying density. *Int J Pharm* 114:1–11, 1995.
6. JE Devereus, JM Newton, MB Short. The influence of density on the gastrointestinal transit of pellets. *J Pharm Pharmacol* 42:500–501, 1990.
7. CW Woodruff, NO Nuessle. Effect of processing variables on particles obtained by extrusion-spheronization. *J Pharm Sci* 61:787–790, 1972.
8. JP Schwartz, NH Nguyen, RL Schnaare. Compaction studies on beads: compression and consolidation parameters. *Drug Dev Ind Pharm* 20:3105–3129, 1994.
9. GP Millili, JB Schwartz. The strength of microcrystalline cellulose pellets: the effect of granulating with water/ethanol mixtures. *Drug Dev Ind Pharm* 16:1411–1426, 1990.
10. HJ Malinowski, WE Smith. Effect of spheronization process variables on selected tablet properties. *J Pharm Sci* 63:285–288, 1974.
11. HJ Malinowski, WE Smith. Use of factorial design to evaluate granulations prepared by spheronization. *J Pharm Sci* 64:1688–1692, 1975.
12. DF Erkoboni, SA Fiore, TA Wheatley, T Davan. The effect of various process and formulation variables on the quality of spheres produced by extrusion/spheronization. Poster presentation, AAPS National Meeting, 1991.
13. M Chariot, J Francès, GA Lewis, D Mathieu, R Phan Tan Luu, HNE Stevens. A factorial approach to process variables of extrusion-spheronization of wet powder masses. *Drug Dev Ind Pharm* 13:1639–1649, 1987.
14. GA Hileman, SR Goskonda, AJ Spalitto, SM Upadrashta. Response surface optimization of high dose pellets by extrusion and spheronization. *Int J Pharm* 100:71–79, 1993.
15. RE O'Connor, J Holinez, JB Schwartz. Spheronization I: Processing and evaluation of spheres prepared from commercially available excipients. *Am J Pharm* 156:80–87, 1984.
16. JE Ojile, CB Macfarlane, AB Selkirk. Drug distribution during massing and its effect on dose uniformity in granules. *Int J Pharm* 10:99–107, 1982.
17. L Hellén, J Yliruusi, P Merkkü, E Kristoffersson. Process variables of instant granulator and spheronizer: I. Physical properties of granules, extrudate and pellets. *Int J Pharm* 96:197–204, 1993.
18. P Kleinebudde, H Lindner. Experiments with a twin screw extruder using a single-step granulation/extrusion process. *Int J Pharm* 94:49–58, 1993.
19. NO Lindberg, C Tufvesson, P Holm, L Olbjer. Extrusion of an effervescent granulation with a twin screw extruder, Baker Perkins MPF 50 D. Influence in intragranular porosity and liquid saturation. *Drug Dev Ind Pharm* 14:1791–1798, 1988.
20. PJ Harrison, JM Newton, RC Rowe. The characterization of wet powder masses suitable for extrusion/spheronization. *J Pharm Pharmacol* 37:686–691, 1985.
21. M Landín, RC Rowe, P York. Characterization of wet powder masses with a mixer torque rheometer. 3. Nonlinear effects of shaft speed and sample weight. *J Pharm Sci* 85:557–560, 1995.
22. L Baert, JP Remon, P Knijff. The influence of extrusion forces and sphere quality on the extrusion forces. *J Pharm Sci* 86:187–192, 1992.
23. L Baert, D Fanara, P De Maesseneire. The influence of extruder and the influence of the extrusion forces. *J Pharm Sci* 86:187–192, 1992.
24. CC Ku, YM Joshi, JS Hsiao. Spheronization—a statistical approach. *J Pharm Sci* 19:1505–1519, 1990.
25. RC Rowe. Spheronization. *Drug Dev Ind Pharm* 11:1885–1895, 1985.
26. PJ Harrison, JM Newton. The extrusion of wet powder masses. *J Pharm Sci* 74:1001–1007, 1985.
27. DC Hicks, HL Freese. Extrusion-spheronization. In: Sellassie, ed. *Pharmaceutical Technology*, 1989, pp. 71–100.
28. PJ Harrison, JM Newton. Spheronization. *J Pharm Sci* 74:1001–1007, 1985.
29. PJ Harrison, JM Newton. The extrusion of wet powder masses. *J Pharm Sci* 74:1001–1007, 1985.
30. JF Pinto, G Buckton, JM Newton. The influence of extrusion and formulation factors on the quality of spheres. *Int J Pharm* 8:1–10, 1981.
31. L Hellén, M Ritala, J Yliruusi. The influence of the radial screen extrusion on the properties of the extrudate. *Int J Pharm* 100:71–79, 1993.
32. C Vaervet, L Baert, PA Remon. The influence of extrusion on pellet quality using a twin screw extruder. *Drug Dev Ind Pharm* 19:39, 1994.
33. L Baert, JP Remon, JAC Remon. The influence of gravity feed extruder and the influence of the extrusion forces. *J Pharm Sci* 86:187–192, 1992.
34. R Shah, M Kabadi, DG Hsiao. The influence of the extrusion/spheronization of the extrusion/spheronization. *Pharm Res* 11:3, 1994.
35. RE O'Connor, JB Schwartz. Spheronization I: Processing and evaluation of spheres prepared from commercially available excipients. *Am J Pharm* 156:80–87, 1984.
36. L Hasznos, I Langer, M Remon. The influence of extrusion characteristics and moisture on the extrusion forces. *J Pharm Sci* 86:187–192, 1992.
37. GA Hileman, SR Goskonda. The influence of extrusion and formulation factors on the quality of spheres. *Int J Pharm* 8:1–10, 1981.
38. L Baert, J Remon. Influence of extrusion forces on the rate from pellets made by extrusion-spheronization. *J Pharm Sci* 86:187–192, 1992.

Tablet granulations composed of 1466–1468, 1972.

Comparative gastrointestinal transit of 114:1–11, 1995.

Influence of density on the gastro- 42:500–501, 1990.

Processing variables on particles ob- 61:787–790, 1972.

Compaction studies on beads: compres- 20:3105–3129, 1994.

Microcrystalline cellulose pellets: the 16:

Spheronization process variables on se- 5–288, 1974.

Factorial design to evaluate granulations 4:1688–1692, 1975.

Shavan. The effect of various process of spheres produced by extrusion/ National Meeting, 1991.

Leu, R Phan Tan Luu, HNE Stevens. of extrusion-spheronization of wet 1639–1649, 1987.

SM Upadrashta. Response surface ion and spheronization. *Int J Pharm*

Spheronization I: Processing and eval- commercially available excipients. *Am J*

Drug distribution during massing and *Int J Pharm* 10:99–107, 1982.

Kristofferson. Process variables of instant Properties of granules, extrudate and

with a twin screw extruder using a *Int J Pharm* 94:49–58, 1993.

Olbjør. Extrusion of an effervescent 50 D. Influence in *Drug Dev Ind Pharm* 14:1791–

The characterization of wet powder on. *J Pharm Pharmacol* 37:686–691,

Extrusion of wet powder masses with a ts of shaft speed and sample weight.

22. L Baert, JP Remon, P Knight, JM Newton. A comparison between the extrusion forces and sphere quality of a gravity feed extruder and a ram extruder. *Int J Pharm* 86:187–192, 1992.
23. L Baert, D Fanara, P De Baets, JP Remon. Instrumentation of a gravity feed extruder and the influence of the composition of binary and tertiary mixtures on the extrusion forces. *J Pharm Pharmacol* 43:745–749, 1991.
24. CC Ku, YM Joshi, JS Bergum, NB Jain. Bead manufacture by extrusion/spheronization—a statistical design for process optimization. *Drug Dev Ind Pharm* 19:1505–1519, 1993.
25. RC Rowe. Spheronization: a novel pill-making process? *Pharm Int* 6:119–123, 1985.
26. PJ Harrison, JM Newton, RC Rowe. The application of capillary rheometry to the extrusion of wet powder masses. *Int J Pharm* 35:235–242, 1987.
27. DC Hicks, HL Freese. Extrusion and spheronization equipment. In: I Ghebre-Sellassie, ed. *Pharmaceutical Pelletization Technology*. New York: Marcel Dekker, 1989, pp. 71–100.
28. PJ Harrison, JM Newton, RC Rowe. Flow defects in wet powder masses. *J Pharm Pharmacol* 37:81–83, 1984.
29. PJ Harrison, JM Newton, RC Rowe. Congergent flow analysis in the extrusion of wet powder masses. *J Pharm Pharmacol* 37:81–83, 1984.
30. JF Pinto, G Buckton, JM Newton. The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronization. *Int J Pharm* 83:187–196, 1992.
31. L Hellén, M Ritala, J Yliruusi, P Palmroos, E Kristoffersson. Process variables of the radial screen extruder: I. Production capacity of the extruder and the properties of the extrudate. *J Pharm Technol Int* 4:50–60, 1992.
32. C Vaervet, L Baert, PA Risha, JP Remon. The influence of the extrusion screen on pellet quality using an instrumented basket extruder. *Int J Pharm* 107:29–39, 1994.
33. L Baert, JP Remon, JAC Elbers, EMG Van Bommel. Comparison between a gravity feed extruder and a twin screw extruder. *Int J Pharm* 99:7–12, 1993.
34. R Shah, M Kabadi, DG Pope, LL Augsberger. Physico-mechanical characterization of the extrusion/spheronization process. Part I: Instrumentation of the extruder. *Pharm Res* 11:355–360, 1994.
35. RE O'Connor, JB Schwartz. Extrusion and spheronization technology. In: I Ghebre-Sellassie, ed. *Pharmaceutical Pelletization Technology*. New York: Marcel Dekker, 1989, pp. 187–216.
36. L Hasznos, I Langer, M Gyarmathy. Some factors influencing pellet characteristics made by an extrusion/spheronization process, Part I: Effects on size characteristics and moisture content decrease of pellets. *Drug Dev Ind Pharm* 18:409–437, 1992.
37. GA Hileman, SR Goskonda, AJ Spalitto, SM Upadrashta. A factorial approach to high dose product development by an extrusion/spheronization process. *Drug Dev Ind Pharm* 19:483–491, 1993.
38. L Baert, J Remon. Influence of amount of granulating liquid on the drug release rate from pellets made by extrusion spheronization. *Int J Pharm* 95:135–141, 1993.

39. LSC Wan, PWS Heng, CV Liew. Spheronization conditions on spheroid shape and size. *Int J Pharm* 96:59–65, 1993.
40. AM Dyer, KA Khan, ME Aulton. Effect of the drying method on the mechanical and drug release properties of pellets prepared by extrusion. *Drug Dev Ind Pharm* 20:3045–3068, 1994.
41. RE O'Connor, JB Schwartz. Spheronization II: Drug release from drug–diluent mixtures. *Drug Dev Ind Pharm* 11:1837–1857, 1985.
42. GP Millili, RJ Wigent, JB Schwartz. Autohesion in pharmaceutical solids. *Drug Dev Ind Pharm* 16:2383–2407, 1990.
43. L Maganti, M Celik. Compaction studies on pellets I. Uncoated pellets. *Int J Pharm* 95:29–42, 1993.
44. JAB Funck, JB Schwartz, WJ Reilly, ES Ghali. Binder effectiveness for beads with high drug levels. *Drug Dev Ind Pharm* 17:1143–1156, 1991.
45. H Linder, P Kleinebudde. Use of powdered cellulose for the production of pellets by extrusion/spheronization. *J Pharm Pharmacol* 46:2–7, 1994.
46. KE Fielden, JM Newton, RC Rowe. The influence of lactose particle size on the spheronization of extrudate processed by a ram extruder. *Int J Pharm* 81:205–224, 1992.
47. TY Chien, NO Nuessle. Factors influencing migration during spheronization. *Pharm Technol* 4:44–48, 1985.

# 12

## Continuous Granulation

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- I. CONTINUOUS PROCESSING
  - A. Introduction
  - B. Batch or Continuous
  - C. Design Requirements
- II. CONTINUOUS GRANULATION
  - A. Continuous Fluid Bed
  - B. Mechanical Continuous
- III. INTEGRATING PRIMARY GRANULATION
- IV. FUTURE CONCEPTS
- V. SUPPLIERS ADDRESS

\*Current affiliation: Novo Nordisk A/S

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## I. CONTINUOUS PROCESSING

### A. Introduction

Continuous processing has long been well established in the food, dairy, and chemical industry for reasons relevant to the large-volume production often found in these industries:

- High throughputs of one or just a few different products
- Ease of automation
- Consistent quality
- Low operating costs

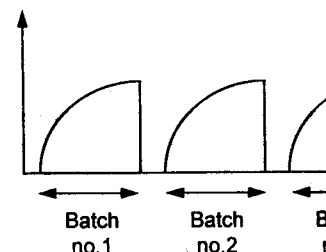
The idea of using continuous processing in secondary pharmaceutical (finished dosage forms) production is not really new, and several individual operations carried out in a pharmaceutical manufacturing facility today, are actually continuous (i.e., milling and sifting, tableting, tablet packaging, and others).

The ideal continuous process is specifically interesting to the pharmaceutical industry because scale-up from pilot plant-to full production-scale can be accomplished by just extending the time the process is running (the core of the equipment does not change). This reduces the time required to introduce a new product to the production site. Despite these advantages, the number of continuous granulation and drying installations in the secondary pharmaceutical industry is still very limited. Some of the reasons for this, may be ascribed to the following:

1. Tradition: The batch processing of a pharmaceutical product is the way the industry has always approached the production process.
2. Know-how: It requires a different approach to run a continuous system than it takes to run a batch system.
3. Registration and good manufacturing practices (GMP): The regulatory authorities in various countries have been skeptical toward new continuous processes. The issue of isolating a batch of product, in case of a recall, has been the main concern, primarily because of the documentation issues (keeping track of the product). The availability of the equipment suitable for manufacturing in the highly regulated environment was another reason for this reluctance to the continuous processing approach. But with the proliferation of validated processes and GMP-conforming hardware, some of the skepticism is disappearing.
4. Capacity and changeovers: Much of the available equipment has not been designed to match the average production mode of secondary manufacturing. Throughputs have been too high, material

## Continuous Granulation

Condition x



**Fig. 1** In batch processing the product quality is achieved through the final mixing of one or more batches.

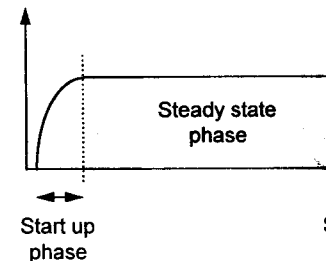
holdup in the equipment is too complicated and expensive.

### B. Batch or Continuous

Although batch processes are desirable for most products to achieve consistent quality, it is possible to switch from either process to a continuous one.

When you consider the continuous process, the material is being processed and continuously mixed, thus eliminating the need for subjecting all of the material to a final mixing phase. However, this is not true. On the other hand, in a particular phase of the process, the material is

Condition x



**Fig. 2** In continuous processing the product quality is achieved in the steady-state phase. Product quality is achieved through different characteristics.

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the large-volume production often

a few different products

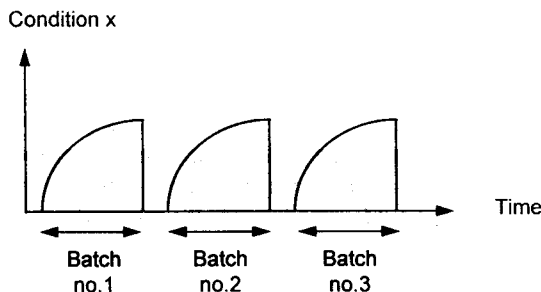
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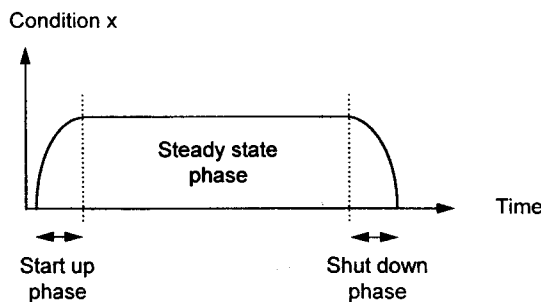
**Fig. 1** In batch processing the conditions are constantly changing. The specified product quality is achieved through backmixing during processing and through a final mixing of one or more batches.

holdup in the equipment is too high, and changeovers and cleanup,  
too complicated and time-consuming.

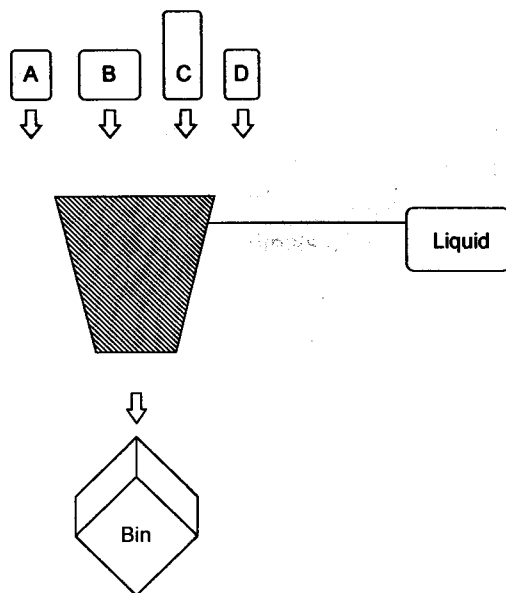
## B. Batch or Continuous?

Although batch processes differ from continuous (Figs. 1 and 2), it is possible for most products to achieve the same characteristics when the product is switched from either processes.

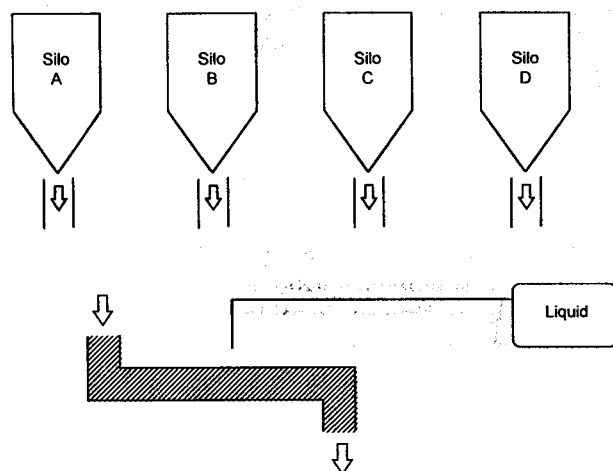
When you consider the mixing in a batch process, all of the material is being processed and constantly mixed at any given time; thereby subjecting all of the material to changing conditions. In the continuous process, however, this is not true. Only a small part of the material is exposed to a particular phase of the process (e.g., spraying) at a given time, and the



**Fig. 2** In continuous processing the conditions and the product quality are constant in the steady-state phase. Product produced during start-up and shut-down will have different characteristics.



**Fig. 3** Material flow in a traditional batch granulation and drying system: Pre-weighed raw materials needed for a certain batch size of finished product are charged into the mixer-granulator-dryer. The dry granulate is sieved and finally collected in a bin or tumbler.

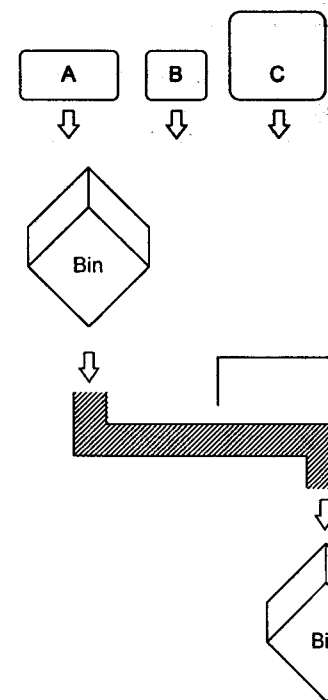


**Fig. 4** Material flow in a fully continuous, large-capacity granulation and drying system: The individual raw materials are continuously fed directly from silos through loss-in-weight feeders into the continuous mixer, granulator, dryer, and sieve. If the product is intended for tableting, tablet presses can be connected to the line.

## Continuous Granulation

process reaches a steady state of a given quality can be enabled and, to some extent, leaving the formulator with many parameters (controlled over

Batch granulation and drying, for example, is well suited for low-quantity ingredients (Fig. 3). However, the systems can even work with large charges the preweighed raw materials.

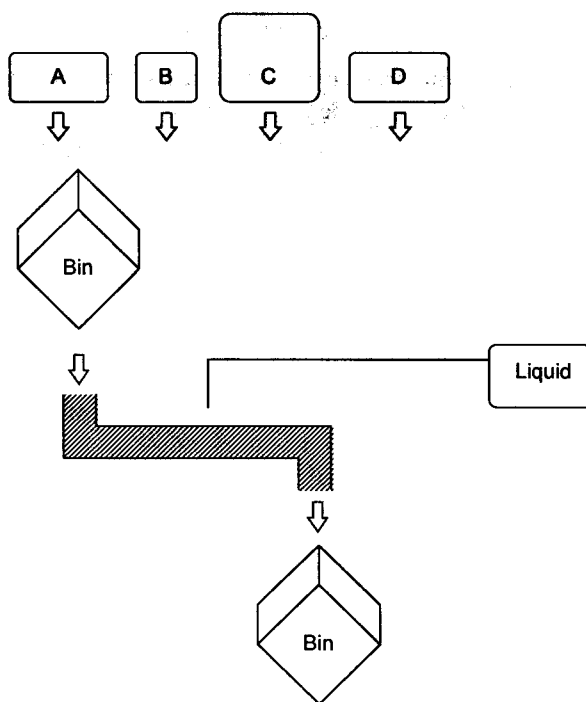


**Fig. 5** Material flow in a continuous granulation and drying system: raw materials needed for a certain batch size of finished product are charged into a bin-blender. After blending, the material is fed into the continuous granulator, dryer, and sieve. The material is then collected in a bin or tumbler and is blended. Seen from the perspective of the formulator, the process does not really differ from a traditional batch process.



process reaches a steady state at which conditions are constant and the product of a given quality can be produced for any length of time. This fact enables and, to some extent, requires the use of more extreme conditions, leaving the formulator with a wider range within which he can choose the parameters (controlled overwetting of difficult to granulate products).

Batch granulation and drying requires only a simple setup and, therefore, is well suited for low-volume products and for products consisting of many ingredients (Fig. 3). Any degree of automation can be applied, and the systems can even work in a manual mode (e.g., the operator manually charges the preweighed raw materials into a high shear or fluid bed granulator).



**Fig. 5** Material flow in a partly continuous granulation and drying system: The raw materials needed for a certain amount of finished product are manually dispensed into a bin-blender. After blending, the powder is continuously fed into the continuous granulator, dryer, and sieve. The dry granulate is finally collected in a bin-tumbler and is blended. Seen from a quality assurance point of view the system does not really differ from a traditional batch setup.

On the other hand, continuous granulators requires accurate-feeding systems for each component and a good control of the discharge rate. To obtain the full benefit from continuous systems they should be set up as fully automated systems (Fig. 4).

To facilitate the change from a batch system to a continuous one, a setup in which processing starts and ends as discrete batches can be employed (Fig. 5). This approach integrates elements from batch management and continuous processing and has part of the robustness and simplicity of a batch system, but the performance of a continuous process. This intermediate approach can be used for a time until sufficient experience has been gathered with the continuous part, or until the manufacturing organization feels more comfortable about continuous processing.

### C. Design Requirements

Several requirements are of special importance to the continuous process technology employed in secondary pharmaceutical manufacturing:

1. **Robust processing:** The process should be able to compensate for usual variations in raw material quality and should be stable, once the steady-state phase is reached.
2. **Minimal material holdup:** Often only small amounts of material are available for laboratory and even pilot plant trials. Therefore, it is important that representative process development can be carried out employing a minimum of material. The simplest and most predictable scale-up is achieved when the same equipment core (essential process part) is used for both laboratory-scale and full-scale production runs (scale-up on time).

A minimal holdup of material is also important to reduce the amount of unacceptable (out-of-specification) material produced during start-up and shut-down of the process (outside the steady-state part of the processes).

3. **Minimal floor space:** Reducing the required processing (GMP) area is important owing to the high capital and running costs tied up in this area of a facility. Through-the-wall installations minimize the required processing areas and are the optimal solutions both from an economic and a GMP point of view.
4. **Quick changeover:** Secondary pharmaceutical operations today are characterized by a multitude of different products produced on the same process lines. Furthermore, through the introduction of just-in-time (JIT) concepts, the lengths of manufacturing campaigns have been cut down resulting in a large number of changeovers.

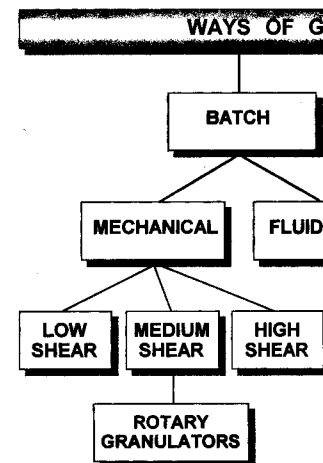
## Continuous Granulation

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## II. CONTINUOUS GRA

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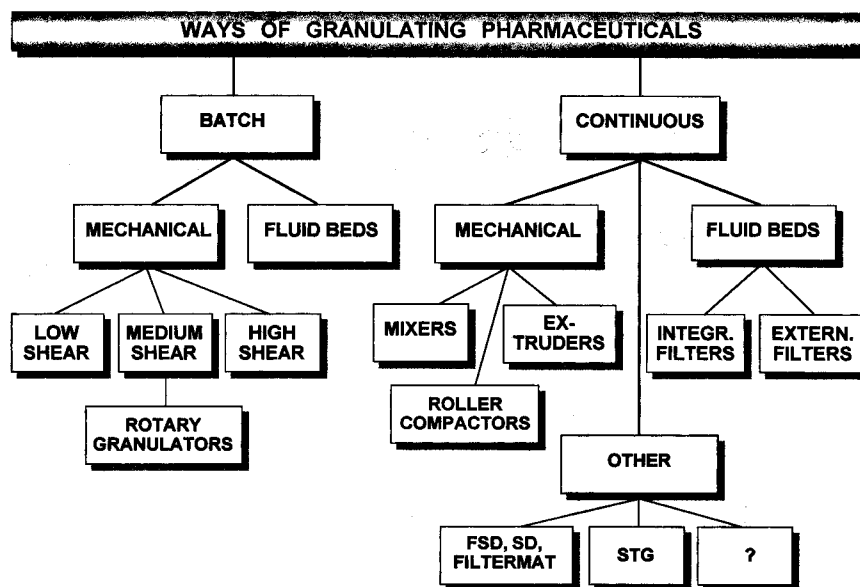
armaceutical operations today are different products produced on the through the introduction of just- ths of manufacturing campaigns a large number of changeovers.

Any equipment—batch or continuous—therefore, should be de- signed to facilitate fast changeover.

5. **Cleanability:** Most of the continuous process equipment was orig- inally designed for non-pharmaceutical processing and was often meant for dedicated manufacturing of a single product. If such a unit is installed in a secondary pharmaceutical facility, the expec- tations of the user will seldom be fulfilled. The cleaning of the entire process train to meet the regulatory requirements would be necessary.

## II. CONTINUOUS GRANULATION TECHNOLOGIES

As can be seen from Fig. 6 the continuous granulation technologies are divided into three main groups:



**Fig. 6** Ways of granulating pharmaceuticals: Granulation processes and equipment can be divided into groups, as shown in the diagram. The two process technologies mainly dealt with in this chapter are the continuous fluid bed granulators with integrated filters and the continuous mechanical mixed granulators. The group called "other" is typically used for producing direct compressible substances: FSD, fluidized bed spray dryer; SD, traditional spray dryer; Filtermat, spray dryer with integrated belt; STG, spray dryer granulator.

1. **Mechanical granulators:** The processes are based on either massing of a moist or melted mixture or on dry compaction.
2. **Fluid bed spray granulators:** Liquids (solutions, suspensions, or melts) are sprayed onto a fluidized dry powder mixture.
3. **Other:** This group includes various processes (e.g., spray drying) frequently used in the primary pharmaceutical industry (fine chemicals) to produce direct compressible substances.

Roller compactors and extruders are described elsewhere in this book, hence, the following will be a brief description of technologies used for primary pharmaceuticals ("other") and a more in-depth description of equipment developed (or modified) for the secondary manufacturing.

## A. Continuous Fluid Bed Granulators

### 1. Introduction

The continuous fluid bed process technology has been in use for more than 30 years, but until recently, none of the systems were designed specifically for pharmaceutical use and, hence, were not common in the industry. However, because of the availability of the new generation of pharmaceutical equipment, the interest in this type of processing is increasing.

### 2. The Process

On the basis of experience from a batch process (batch fluid bed granulation is described elsewhere in this book), changing to a continuous mode poses the least number of problems.

Most continuous fluid beds will have five or more functional zones (the zones are not necessarily mechanically separated from each other):

1. Product in-feed zone
2. Product mixing and preheating zone
3. Spraying zone
4. Drying and cooling zone
5. Discharge zone

### 3. Product Flow

The way a product flows through a continuous fluid bed is extremely important to the final product quality. The flow control mechanisms should assure a consistent, homogeneous transport of all the present particle sizes to avoid segregation and heat damage. If mechanical barriers (baffles) are used, it is especially important that larger particles (lumps) are moved. The flow can be described as either a "plug flow" or a "backmix" flow.

## Continuous Granulation

A plug flow (Fig. 7) from the product in-feed pipe). Because the product requires a well-controlled temperatures. If controlled potential for well-defined pro

In a backmix (Fig. 8) agglomerated material. The pathway is not well de particles will have a wide spr bed during the whole proc benefit from being process material is mixed with part A backmix process is robu compensated for through r to the wide residence time as satisfactory as in a perf

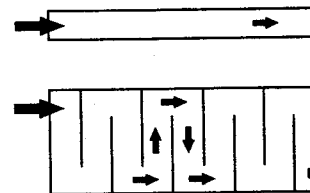
The degree of plug Peclet number (Eq. 1):

$$N_P = \frac{(b)}{(\text{bed width}) \times (v)}$$

The Peclet number  $N_P$  in a fluid bed processor. A plug flow, whereas a Pec (seen in a batch fluid).

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**Fig. 7** Product flow in two width ratio achieved by cho the use of partition walls.

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A plug flow (Fig. 7) is characterized by the product moving directly from the product in-feed point toward the discharge point (like liquid in a pipe). Because the product residence time distribution is short, the process requires a well-controlled powder feed rate, liquid spray rate, and temperatures. If controlled properly, a plug flow processor offers the highest potential for well-defined product characteristics.

In a backmix (Fig. 8) system, incoming powder is mixed with already agglomerated material. The general flow is toward the discharge point, but the pathway is not well defined, and the retention time for individual particles will have a wide spread (theoretically a particle could remain in the bed during the whole process). Products (feeds) that are difficult to fluidize benefit from being processed in backmix system because the non-processed material is mixed with partly processed material when entering the fluid bed. A backmix process is robust because the effect of variations in feed rate are compensated for through mixing with partially processed material. Owing to the wide residence time distribution, the product quality is potentially not as satisfactory as in a perfect plug flow bed.

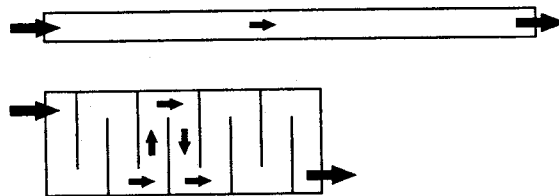
The degree of plug flow and back mix can be described using the Peclet number (Eq. 1):

$$N_P = \frac{(\text{bed length}) \times (\text{powder feed rate})}{(\text{bed width}) \times (\text{powder per m}^2 \text{ bed}) \times (\text{backmix coefficient})} \quad (1)$$

The Peclet number  $N_P$  is used to characterize the degree of plug flow in a fluid bed processor. A high Peclet number indicates a high degree of plug flow, whereas a Peclet number of zero indicates complete backmix (seen in a batch fluid).

The product can be moved in a given direction by:

a. *Vibrating the Fluid Bed.* The advantage of this principle is that product can be transported through the bed using less air than needed in a



**Fig. 7** Product flow in two different plug flow systems. Both have a high length/width ratio achieved by choosing either a long and narrow processor (pipe) or by the use of partition walls.

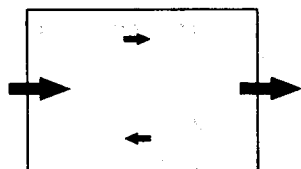


Fig. 8 Product flow in a backmix system with a low length/width ratio.

stationary fluid bed. The system is very flexible and products with wide particle size distributions (of up to 1:100) can be fluidized. Attrition to already-formed agglomerates is low during processing but one should bear in mind that it can occur later on during further handling (e.g., pneumatic conveying). A disadvantage of the vibrating fluid bed is the design restrictions put on the system owing to flexible connections and moving parts.

*b. Directing the Airflow.* Through the use of air distributor plates with openings (gills) that create directed jets, it is possible to move the product in a controlled manner through the processing zones. The absence of moving parts and flexible connections simplifies the design and enables pressure-shock-resistant construction. Attrition of the formed granules during processing is higher than in the vibrating fluid bed, but the final product is mechanically more stable.

*c. Sloped Air Distributors.* A fluidized material behaves similarly to a liquid. If the product in-feed is placed at a higher point than the product discharge, the general flow will be toward the discharge. The sloped design is simple and can create a directional flow, but it will also unfortunately give a fluidization that is not homogeneous.

#### 4. Nozzle Arrangement

Binder liquid is introduced through nozzles placed either above the fluidized layer (spraying downward), below (spraying upward) or both. Difficult-to-granulate products can most often be processed with better result in a bottom-spray mode than in top-spray owing to the proximity of the nozzles to the product (local overwetting causes the building of stronger agglomerates).

As in batch fluid bed processors, externally mixed two-fluid nozzles are the first choice in the continuous fluid bed processes because they offer the highest flexibility in spray rates and droplet sizes.

#### 5. Process Air Filtration

After the process air has passed through the granulation zone, it picks up some fine particles. These are removed by a filter, and the air is returned to the continuous fluid beds used in the granulation process. In the pharmaceutical industry, external cyclones are often used for this purpose.

In secondary pharmaceutical granulation, the product consists of several components. The granulation process integrates filters (bag filters, cartridge filters, etc.) into the fluidized layer (as known in the pharmaceutical industry) to enable inspection of the product.

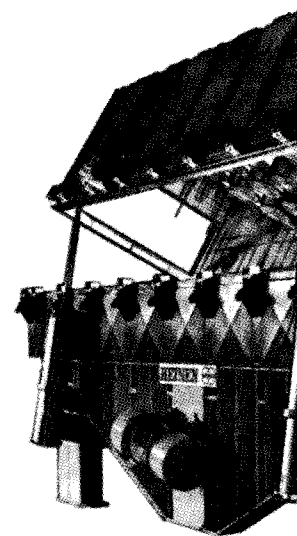
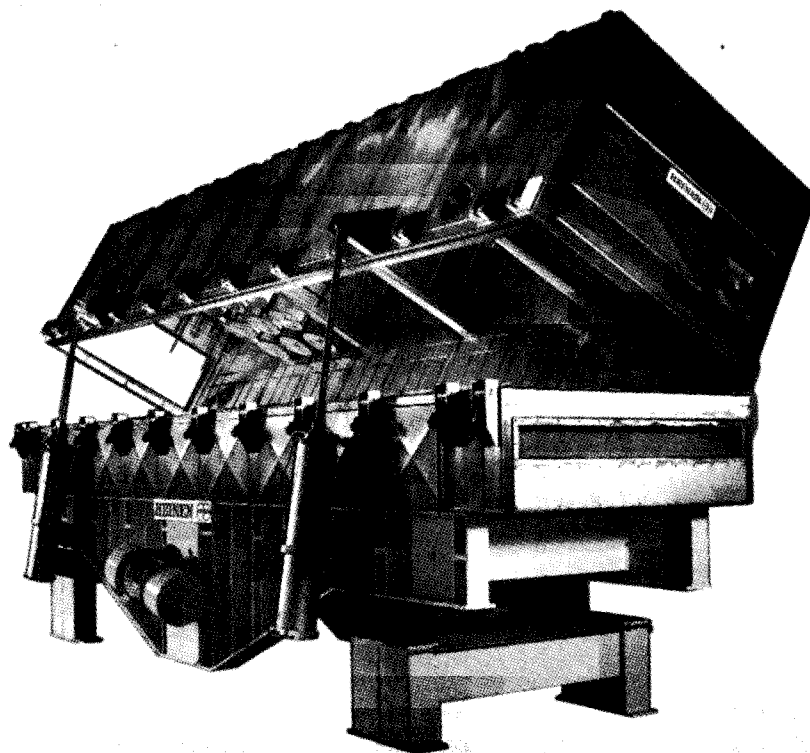


Fig. 9 Heinen continuous granulation machine (used in many pharmaceutical plants).

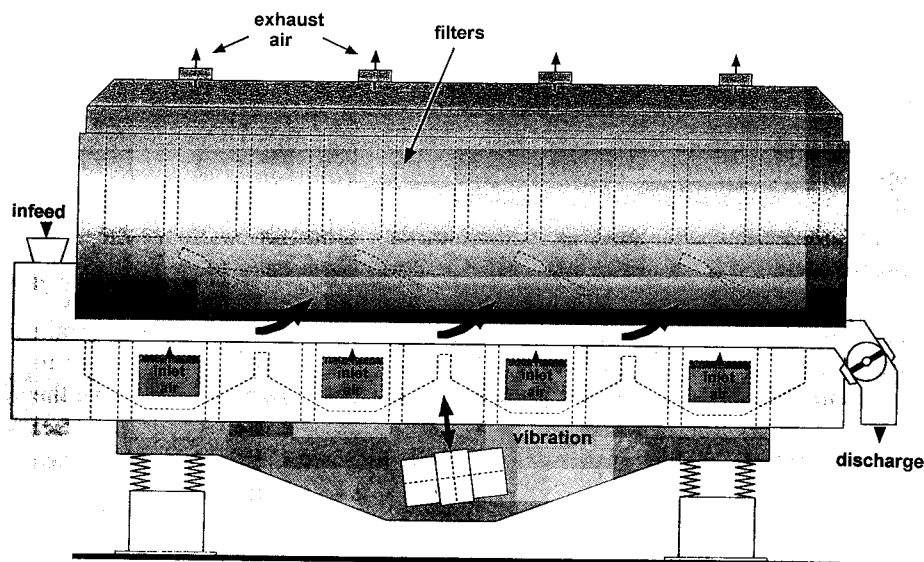
### 5. Process Air Filtration

After the process air has passed through the fluidized product layer, it picks up some fine particles. These elutriated particles should be separated from the air and returned to the fluid bed for further processing. In traditional continuous fluid beds used in industries other than the pharmaceutical industry, external cyclones or external bag filters have been preferred.

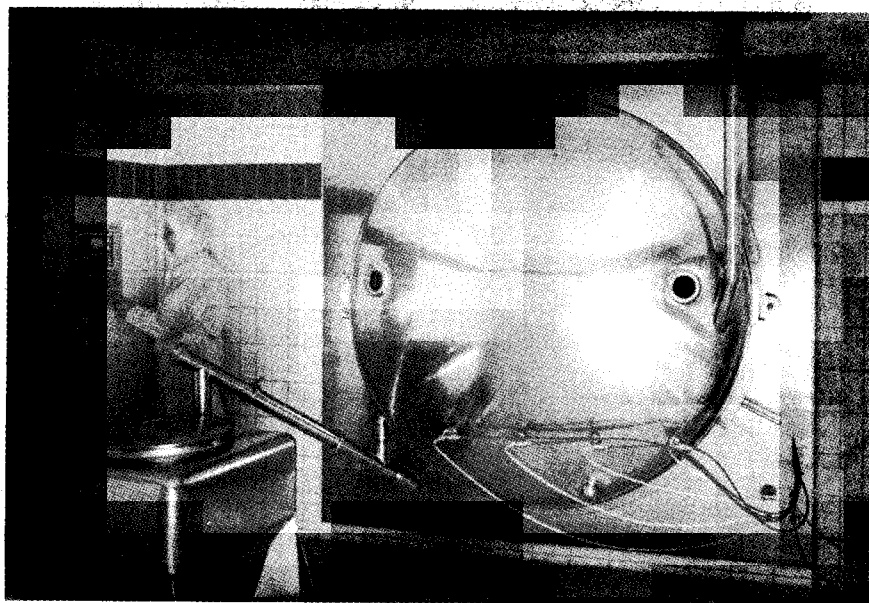
In secondary pharmaceutical manufacturing in which the typical product consists of several components, it is not acceptable to separate a certain fraction of the product (the fines). The preferred solution, therefore, is to integrate filters (bag filters or cartridges) in the free-board directly above the fluidized layer (as known from batch fluid beds). The use of stainless steel cartridge filters enables installation of clean-in-place (CIP) systems.



**Fig. 9** Heinen continuous fluid bed. (Courtesy of A. Heinen GmbH, Varel, Germany.)

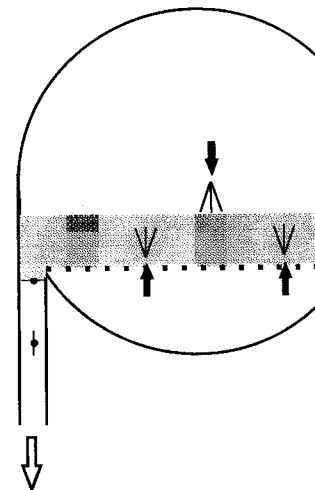


**Fig. 10** Heinen continuous fluid bed processor: This vibrating fluid bed is designed for spray granulation, drying, and cooling. It is based on a traditional square fluid bed, but is designed for the pharmaceutical industry. It has integrated cartridge filters and has several separate air inlets and outlets. (Courtesy of A. Heinen GmbH, Varel, Germany.)



**Fig. 11** Conti Pharm fluid bed processor. (Courtesy of Aeromatic-Fielder AG, Bubendorf, Switzerland.)

## Continuous Granulation



**Fig. 12** Conti Pharm fluid bed processor: This vibrating fluid bed is designed for spray granulation, drying, and cooling. It is based on a traditional square fluid bed, but is designed for the pharmaceutical industry. It has integrated cartridge filters and has several separate air inlets and outlets. (Courtesy of Aeromatic-Fielder AG, Bubendorf, Switzerland.)

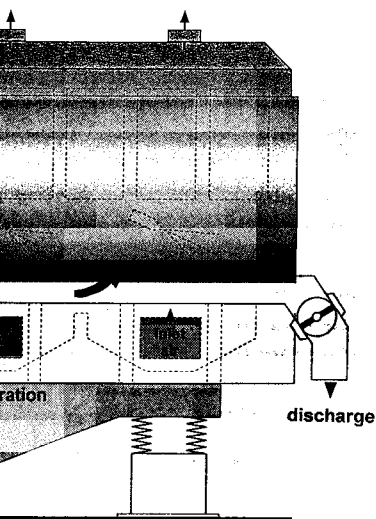
### 6. Feeding and Discharge

During the start-up phase the empty bed has to be filled. During the steady-state phase, the bed should be continuously filled. Finally, the bed should be discharged.

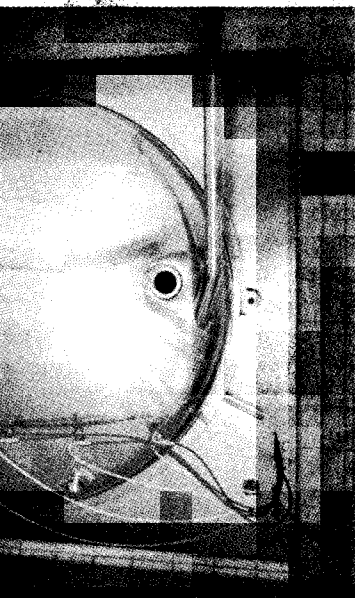
The in-feed and discharge systems are simple double-valve systems. The capacities should be sufficient for the start-up and discharge phases.

The fluidized layer height is determined by the pressure drop across the layer (pressure drop).

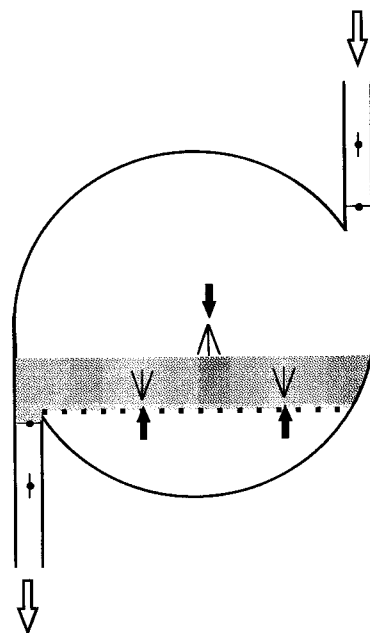




This vibrating fluid bed is designed based on a traditional square fluid bed. It has integrated cartridge filters with cip. (Courtesy of A. Heinen GmbH, Varel,



(Courtesy of Aeromatic-Fielder AG,



**Fig. 12** Conti Pharm fluid bed processor: This stationary fluid bed is based on two convex parts (installed through-the-wall) of which one is installed in the technical area and the other in the processing area. It is designed specifically for pharmaceutical manufacturing and has integrated cartridge filters with cip. The system is pressure-shock-resistant to 10 bar. The filters and the airflow are not shown. (Courtesy of Aeromatic-Fielder AG, Bubendorf, Switzerland.)

## 6. Feeding and Discharging

During the start-up phase of the continuous fluid bed granulation process, the empty bed has to be filled with powder to a certain level (bed height). During the steady-state phase this bed height is maintained constant and, finally, the bed should be completely emptied during shut-down.

The in-feed and discharge of product can take place either through a simple double-valve system or a rotary valve. The in-feed and discharge capacities should be sufficiently high to assure short start-up and shut-down phases.

The fluidized layer height is kept constant by simply monitoring the pressure drop across the layer (the discharge rate is controlled by the pressure drop).

## 7. Examples of Continuous Fluid Bed Processors

A large number of suppliers produce continuous fluid beds, but only a few have designed systems suitable for secondary pharmaceutical manufacturing (Figs. 9–12).

## B. Mechanical Continuous Granulators

### 1. Introduction

For various reasons (e.g., final product density, nonfluidizable starting materials, or other) fluid bed dryers are often combined with mechanical granulators.

A number of parameters and design features are of special importance when characterizing granulators:

*a. Product Residence Time.* Some processors are similar in their action to batch, high shear granulators, with a massing time of several minutes. Others have an extremely short contact time (seconds) with the binder and are actually just wetting the powder. The longer the contact time is, the less critical is the process, but at the same time, the size of the equipment will increase, and product holdup will be high.

*b. Energy Input.* Extruders and high shear granulators introduce the highest amount of energy and, at the same time, have the longest contact time. They produce dense granulates.

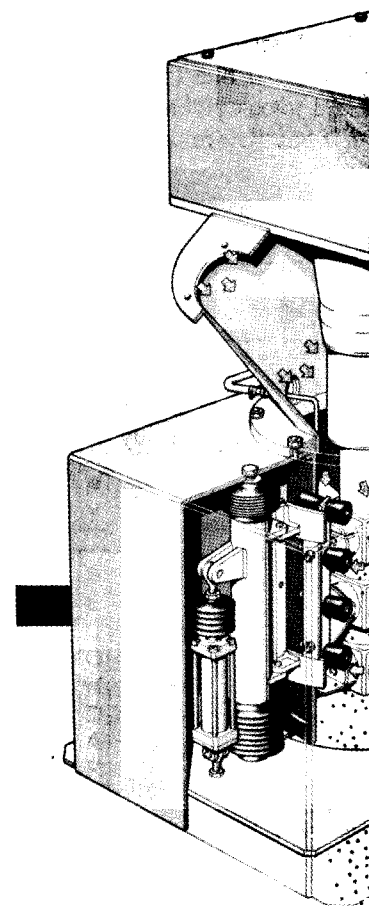
*c. Product Holdup.* A small amount of product being processed at a given time facilitates process evaluation, reduces waste, and allows processing of a small volume of product using continuous granulation.

Continuously granulated material is normally dried in continuous fluid bed dryers of the backmix type as they provide robust processing through a powdering effect (by mixing the incoming wet granulate with partly dried material) of the wet and sometimes sticky granulate.

### 2. Examples of Mechanical Continuous Granulators

As with the continuous fluid beds, only a few suppliers have developed continuous granulators specifically for the secondary pharmaceutical manufacturing.

Figures 13–15 are examples of equipment used in pharmaceutical wet granulation.



**Fig. 13** Schugi mixer–agglomerator enclosing a rotating shaft (1000 rpm) are fed by the top inlets and granules are discharged from the bottom of the chamber. Material residence time is 10–15 min. B. V., Lelystad, The Netherlands.

### Processors

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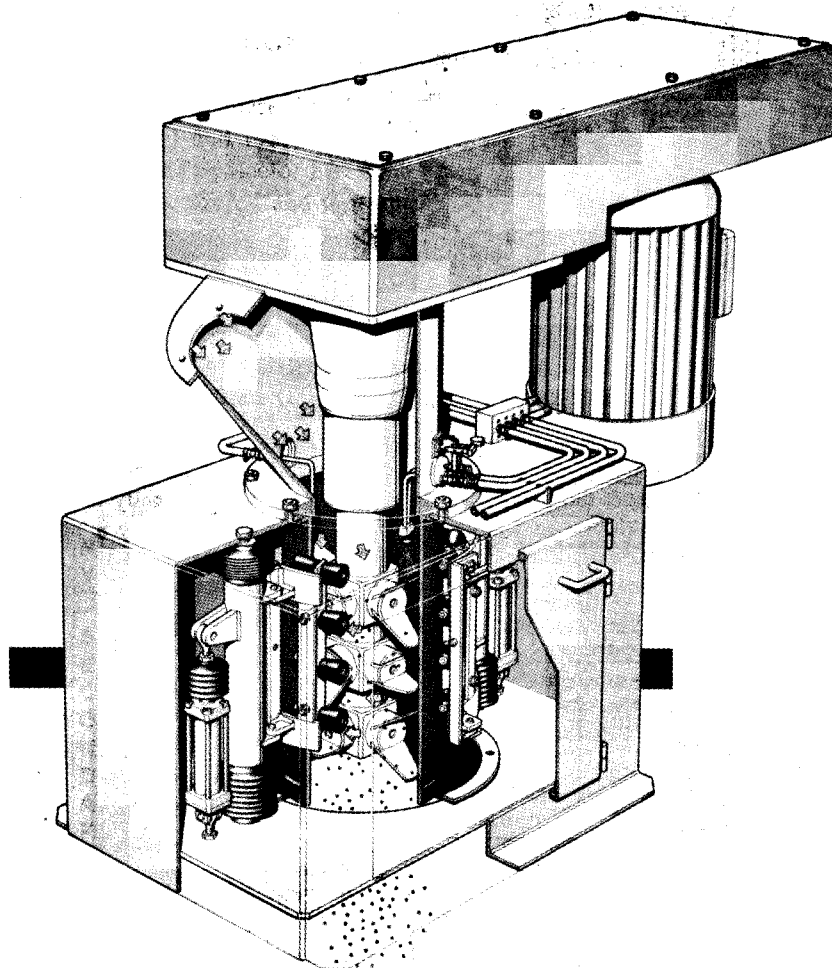
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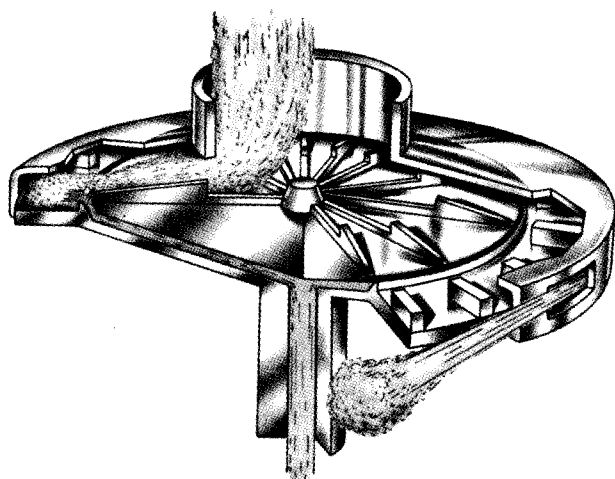


**Fig. 13** Schugi mixer-agglomerator: It consists of a vertical cylindrical chamber enclosing a rotating shaft (1000–3500 rpm) with several protruding knives. Powders are fed by the top inlets and granulation liquids through injectors in the upper portion of the chamber. Material residence time is about 1 s. (Courtesy of Hosokawa Schugi B. V., Lelystadt, The Netherlands.)

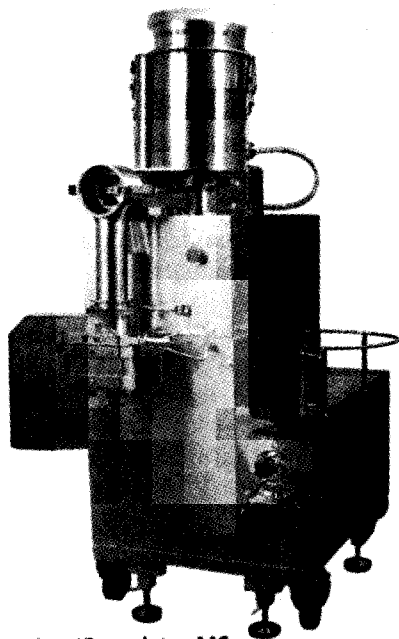
## Continuous Granulation

### III. INTEGRATING PRIMARY PRODUCTION

Traditionally, there has been a clear distinction between the primary (chemicals) and the secondary (pharmaceuticals) sectors. The secondary sector has more complex processes than they were offered and then more

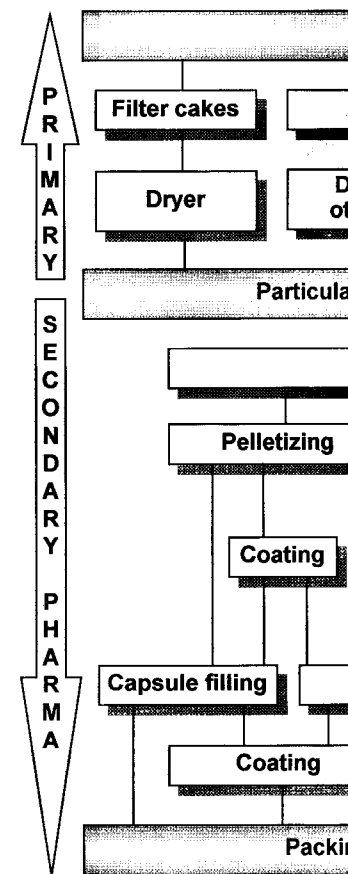


**Fig. 14** Nica M6 turbine mixer and granulator: Powder is fed from above and is dispersed in the high-speed turbine. Granulation liquid is introduced from below the inner turbine wheel and meets the powder at the edge, where they instantly mix. Product holdup is very low (less than 100 g in the process stream). Capacity is up to 360 kg/h. (Courtesy of Aeromatic-Fielder Ltd. Eastleigh, United Kingdom.)



Mixer/Granulator M6

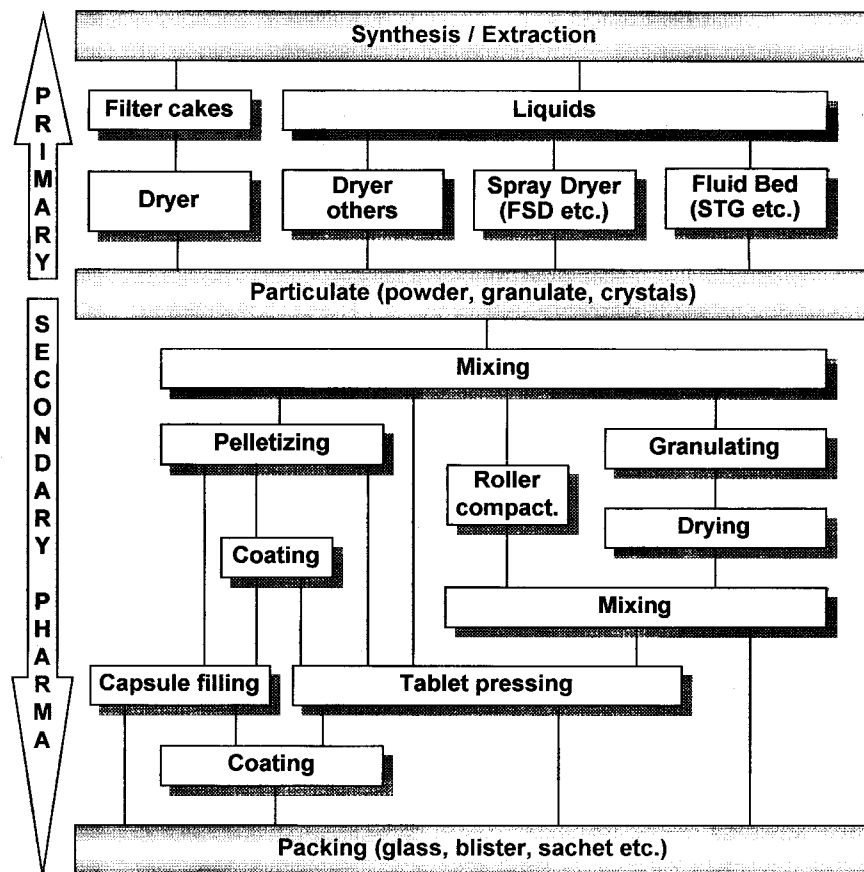
**Fig. 15** Nica M6 turbine mixer and granulator. (Courtesy of Aeromatic-Fielder Ltd. Eastleigh, United Kingdom.)



**Fig. 16** Pharmaceutical solid dosage forms manufacturing routes from manufacturing of raw materials to finished product. The border line between primary and secondary is defined as it once was.

### III. INTEGRATING PRIMARY AND SECONDARY PRODUCTION

Traditionally, there has been little interaction between the primary (fine chemicals) and the secondary (finished products) pharmaceutical industry. The secondary sector has most often accepted substances (e.g., powders) as they were offered and then modified (granulated) them. Today the bounda-



**Fig. 16** Pharmaceutical solids processing: The diagram shows the processing routes from manufacturing of raw materials to the final solid-dosage forms. The border line between primary and secondary pharmaceutical is no longer as well defined as it once was.

ries of separation from both sectors are disappearing, and this could lead to major changes in the way pharmaceutical products are produced.

Regulatory authorities have mandated that the producers of bulk chemicals must fulfill basically the same GMP regulations as the dosage form manufacturer has done for many years. As the primary industry adapts to the new standards, it will be in a position to produce products (granulates, tablets, and such) that today are produced in secondary facilities. For many products, this could cut the total manufacturing costs substantially. Figure 16 describes the overall processing routes for solid pharmaceuticals.

The costs of producing a direct compressible substance are only slightly higher than the costs of producing a simple powder. Direct compression has therefore become the preferred route for many tableted products. Vitamins and paracetamol (acetaminophen) are examples of drugs that already can be purchased virtually ready for tableting ("drum-to-hopper" products).

#### IV. FUTURE CONCEPTS

The role of secondary pharmaceutical manufacturing has changed since the late 1980s. Today, manufacturing is seen as a strategic area that can contribute substantially to the cost-cutting measures necessary to maintain the required profit margins. Except for a limited number of strategic products, manufacturing will be out-sourced to companies with efficient and specialized high-quality production capabilities.

Highly efficient production facilities will become a must, and the lifetime of processing equipment and technologies will decrease. At the same time, more of the capital available in pharmaceutical companies will be employed in research and development and marketing, and the companies will be reluctant to tie up capital in production facilities.

All this leads to a requirement for highly efficient, but low-cost facilities and will call for new concepts. One facility design that could turn out to be a long-term solution is based on a setup known from oil refineries, in which the processes are totally contained. This eliminates the requirement for a surrounding "GMP area."

Batch processing will continue to be important, but continuous processing will increase its share. Even with the available continuous process technology, it makes good sense to consider the continuous processing for pharmaceutical granulation. The change will further accelerate when new

#### Continuous Granulation

generations of continuous processing with minimal (zero) product hold-up. This will produce "product-by-design" without the need for doing a minimum of experiments.

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Germany

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Manufacturing has changed since the 1960s a strategic area that can conserve resources necessary to maintain the small number of strategic products, companies with efficient and specialized

will become a must, and the life-cycle costs will decrease. At the same time pharmaceutical companies will be required to market, and the companies will need to invest in new production facilities.

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generations of continuous process technology are introduced, developed for minimal (zero) product holdup ("processing-in-a-pipe"), and able to produce "product-by-design" (predictable product characteristics achieved using a minimum of experimental work).

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# 13

## Sizing of Granulation

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## I. INTRODUCTION

Tablets are the most frequently administered solid oral dosage forms in contemporary practice. Tablets consist of mixture of powders or granules that are compacted in the die of a tablet press. Even though popularity of directly compressible materials has increased, many powders are granulated to overcome the difficulties in obtaining an acceptable tablet dosage form and meeting the product specifications. The most challenging task in a tableting process is to achieve a constant volume of homogeneous mixture flowing into the tablet die cavity. Unfortunately, most powder materials do not have inherent flow properties. This, in turn, places demand on changing the physical characteristics of the powder or improving the design of the tablet press [1]. Therefore, granulation becomes an integral part of a pharmaceutical process that attempts to improve powder flow characteristics.

The granule properties play a pivotal role in the final performance of a tablet; for example, granule size can affect the flowability and hence the average tablet weight and weight variation and drying rate kinetics of wet granulations. The effect of granule size and size distribution on final blend properties and tablet characteristics is dependent on formulation ingredients and their concentration as well as the type of granulating equipment and processing conditions employed. Therefore, granulation and sizing of granulation become critical unit operations in the manufacture of oral dosage forms [2,3]. To some extent, the same requirements are necessary for capsule manufacture; especially when the drug is bulky or has poor flow properties or in the newer high-speed capsule-filling machines where limited compaction occurs.

Few materials used in the manufacture of pharmaceutical dosage forms exist in the optimum size, and most materials must be reduced in size at some stage during production. The advantages of sizing of granules in tablet formulation development are as follows:

1. Mixing and blending of pharmaceutical ingredients are easier and more uniform if the ingredients are of approximately the same size and distribution.
2. Improving color or active ingredient dispersion; milling may reduce the tendency for mottling and, hence, the uniformity of color from batch to batch.

## Sizing of Granulation

3. Wet milling produces uniform and
4. Improving uniform particle size distribution.
5. Enhancing flow properties and content uniformity.
6. Increasing surface area and the dissolution rate.

### Size reduction alone

There are some disadvantages of size reduction. Some of the characteristics of a dosage form, such as polymorphic form and increase in surface energies, may be affected. Optimizing the manufacture of a dosage form not only to characterize the effect on the manufacturing process, but also to what extent, milled, and to what extent,

The objective of this process is to achieve a uniform size distribution after drying in a wet granulation process. The objective of this process is to achieve a uniform size distribution for obtaining uniformly sized granules. A full discussion of the process is beyond the scope of this paper. The process will accentuate the various factors that affect the process, their merits and demerits, process, scale-up factors, and development and optimization.

## II. THEORY OF COMMINUTION

Comminution, or size reduction, is the process of reducing the size of particles or aggregates. The theory of comminution is based on the understanding of the mechanism of particle size reduction. The reduction of particle size through comminution is dependent on the material to be crushed. The material may be brittle, yielding, with consequent granulation, or elastic, with consequent rebound. The yield point, at which the material would neither rebound nor flow, is the point at which solids lie somewhere between brittle and viscous properties.

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3. Wet milling produces uniformly sized wet granules, which promotes uniform and efficient drying.
4. Improving uniformity of dosage units by virtue of uniformity of particle size distribution and reduction in the segregation of the mix.
5. Enhancing flow properties, which reduces the weight variation and content uniformity.
6. Increasing surface area due to particle size reduction may enhance the dissolution rate and, thereby, the drug's bioavailability.

Size reduction alone is not the panacea for all tableting problems. There are some disadvantages to size reduction that may affect the final characteristics of a dosage form, such as degradation of the drug, a change in the polymorphic form as a result of the excessive heat generated; or increase in surface energies, leading to agglomeration, and so on. Hence, in optimizing the manufacture of pharmaceutical dosage forms, it is important not only to characterize the formulation ingredients, but also to study their effect on the manufacturing process (i.e., whether a granulation should be milled, and to what extent, based on the final product specifications).

The objective of this discussion is to focus on sizing of granulation after drying in a wet granulation process. However, a process of wet milling for obtaining uniformly sized granules for uniform drying will also be addressed. A full discussion of the theories of comminution or equipment description is beyond the scope of this chapter. However, the text of this chapter will accentuate the various types of equipment used in size reduction process, their merits and demerits, and variables affecting the size reduction process, scale-up factors, and relevant case studies to be considered in the development and optimization of tablet and capsule manufacture.

## II. THEORY OF COMMUNITION OR SIZE REDUCTION

Comminution, or size reduction, is the mechanical process of reducing the size of particles or aggregates. There is as yet only a meager basic understanding of the mechanism and quantitative aspects of milling [4,5]. Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to this stress by yielding, with consequent generation of strain. In the case of a brittle substance, complete rebound occurs on release of applied stress at stresses up to the yield point, at which fracture would occur. In contrast, plastic material would neither rebound nor fracture. The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties.



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Although the milling process can be described mathematically [6-8], its theory has not been developed to the point at which the actual performance of a mill can be predicted quantitatively. Three fundamental laws (Kick's law, Rittinger's law, and Bond's law) have been proposed to relate size reduction to a single variable: the energy input to the mill. None of the energy laws apply well in practice [9]. Generally, laboratory testing is required to evaluate the performance of a particular piece of equipment; however, a work index and grindability index have been used to evaluate the mill performance [5]. The efficiency of milling process is influenced by the nature of the force, as well as by its magnitude. The rate of application of force affects comminution, for there is a lag time between the attainment of maximum force and fracture. Often materials respond as a brittle material to fast impact and as a plastic material to a slow force.

### III. PROPERTIES OF FEED MATERIALS AFFECTING THE SIZING PROCESS

The milling or sizing process is affected by a variety of factors and has a direct effect on the quality of the final product. The properties of feed material and the finished product specifications, determine the choice of equipment to be used for the process of comminution. The properties of feed material include melting point, brittleness, hardness, and moisture content. The desired particle size, shape, and size distribution must also be considered in the selection of milling equipment.

Materials can be classified as hard, intermediate, soft, or fibrous (e.g., glycyrrhiza and rauwolfia) based on Moh's scale. Fibrous materials require cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. Before selecting and optimizing a size-reduction process, one needs to know the properties of material and the characteristics of a mill. The important material properties are as follows [5,10]:

1. *Toughness*: Is the material's resistance to the propagation of cracks. Reduction of the particle size of tough material is difficult, but can sometimes be made easier by cooling the material, thereby diminishing its tendency to exhibit plastic flow and making it more brittle.
2. *Brittleness*: The opposite of toughness. Size reduction poses no problems except if the amount of fines are to be controlled.
3. *Abrasiveness*: This is an important factor because abrasive materials can wear mill parts and screens; hence, metal contamination may be a problem.

4. *Cohesive/Adhesiveness*: Particles sticking together or to machine surfaces, is often dependent on moisture content and particle size. Problems with moisture content can be mitigated by drying the material or resorting it to a wet size-reduction process.
5. *Melting point*: This is critical because considerable heat is generated in size reduction. High temperatures generated can cause melting of the drug, blinding of the screen, or can degrade heat-sensitive materials.
6. *Agglomeration tendency*: This tendency can be counteracted by drying the material either before or during the size reduction. In some cases, mixing with other ingredients during milling might be helpful. Generally, materials having a strong tendency to agglomerate are wetted before milling.
7. *Moisture content*: A moisture content above 5% can usually lead to agglomeration or even liquefaction of the milled material. Hydrates will often release their water of hydration under high temperatures and may require cooling or low-speed milling.
8. *Flammability and explosiveness*: A measure of how readily a material will ignite or explode. Explosive materials must be processed in an inert gas atmosphere.
9. *Toxicity*: This has little influence on the selection of mill itself; however, it must be considered in determining operator safety, containment, and setup for this type of material.

#### IV. CRITERIA FOR SELECTION OF A MILL

The selection of equipment is determined by the characteristics of the material, the initial particle size, and the degree of the desired size of the milled product; that is, coarse, medium, or fine.

The criteria for selection of a mill includes the following [4]:

1. *Properties of feed material*: size, shape, moisture content, physical and chemical properties, temperature sensitivity, grindability
2. *Product specifications*: size, particle size distribution, shape
3. *Versatility of operation*: wet and dry milling, rapid change of speed and screen, safety features
4. *Scale-up*: capacity of the mill and production rate requirements
5. *Dust control*: loss of costly drugs, health hazards, contamination of plant
6. *Sanitation*: ease of cleaning and sterilization

#### Sizing of Granulation

7. *Auxiliary equipment*: ing, stage reduction
8. *Batch or continuous*
9. *Economic factors*: cupied, labor cost

After consideration of the problem, it is suggested that a variety of product results such as shape, size, and production. In addition, to the material (e.g., screen, speed, and rotation) considered for special material, a closed system supplied with air in milling is converted into a system that build up in the milling chamber. The heat generated during a mill can be used for harder and denser material milled using a coarser screen. Screening the discharge and the milling (closed circuit mill) the air or gas (carbon dioxide) the product before processing which the product passes. A mill will add to the cost of processing the material, it may be fed

#### V. CLASSIFICATION OF

Most size-reduction equipment which forces are applied; compression (Table 1). A general class: a hammer mill machine to mill a crystalline material. The reduction of the granules can be on the energy input into the energy mills available for pharmaceutical industry for the extremely inefficient unit operation being used in the actual size reduction. The characteristics of the material

sticking together or to machine moisture content and particle size. can be mitigated by drying the size-reduction process.

cause considerable heat is generated, temperatures generated can cause the screen, or can degrade heat-

tendency can be counteracted by or during the size reduction. In ingredients during milling might be ng a strong tendency to agglom-

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A measure of how readily a ma- sive materials must be processed

on the selection of mill itself; in determining operator safety, rpe of material.

## MILL

by the characteristics of the ma- e of the desired size of the milled

cludes the following [4]:

shape, moisture content, physical ure sensitivity, grindability cle size distribution, shape ry milling, rapid change of speed

d production rate requirements s, health hazards, contamination

sterilization

7. *Auxiliary equipment*: cooling system, dust collectors, forced feed- ing, stage reduction
8. *Batch or continuous operation*
9. *Economic factors*: equipment cost, power consumption, space oc- cupied, labor cost

After consideration of the foregoing factors for a specific milling prob- lem, it is suggested that a variety of mills should be evaluated for optimum product results such as shape of granules or scalability from laboratory to production. In addition, to the standard adjustments of the milling process (e.g., screen, speed, and rotor design) other techniques of milling may be considered for special materials. Hygroscopic materials can be milled in a closed system supplied with dehumidified air. As bulk of the energy used in milling is converted into heat, heat-sensitive materials, or hard materials that build up in the milling chamber may melt, decompose, or explode with heat generated during a milling process. A two- or multistep milling process can be used for harder and difficult-to-grind materials. Materials can also be milled using a coarser screen, and the material can then be recycled by screening the discharge and returning the oversized material for a second milling (closed circuit mill) Alternatively, the next solution involves chilling the air or gas (carbon dioxide or nitrogen) that transports the product, cool the product before processing, or cool the comminuting chamber through which the product passes. A chiller is necessary for all of these options and will add to the cost of processing [11]. If this is not sufficient to embrittle the material, it may be fed to the mill simultaneously with dry ice.

## V. CLASSIFICATION OF MILLS

Most size-reduction equipment may be classified according to the way in which forces are applied; namely, impact, shear, attrition, and shear-compression (Table 1). A given mill may operate successfully in more than one class: a hammer mill may be used to prepare a 16-mesh granulation and to mill a crystalline material to a 120-mesh powder. The mills used for size reduction of the granules can be divided into two primary categories based on the energy input into the process. Even though there are several high-energy mills available for size reduction, only a few are used in the pharmaceutical industry for the wet- or dry-sizing process. Milling is an extremely inefficient unit operation, with only 1–2% of the applied energy being used in the actual size reduction. Milling efficiency is dependent on the characteristics of the material used and type of mill employed.

A. Low-Energy Mills

1. Hand Screen

- Size reduction occurs
- They are made of wire cloth stretched
- They are available for granulation, m
- They are most widely used for granulation of wet and dry gran

2. Oscillating–Rotary G

- They consist of an
- and the material is
- rotary motion of the
- Size reduction is f
- Speed, rotary or o
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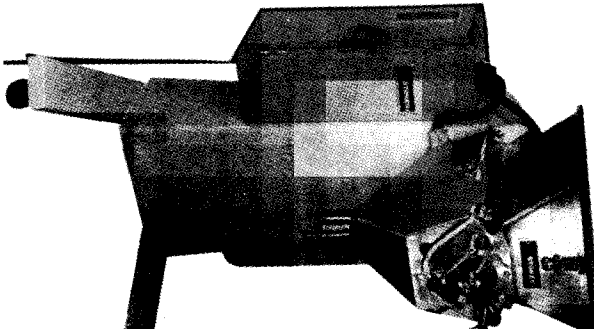


Fig. 1 Oscillating granulator

Table 1 General Characteristics of Various Types of Mills

Mechanism of action	Example	Particle size	Recommended for	Not recommended for
Impact	Hammer mill	Moderate to fine	Brittle and dry material	Fibrous, sticky, low-melting substances
Shear	Extruder and Hand screen	Coarse	Deagglomeration, Wet granulation	Dry material, hard, abrasive materials
Attrition	Oscillating granulator	Coarse to moderate	Dried granulation	Wet granulation, abrasive materials
Shear–compression	Comil	Moderate to coarse	Wet, dry granulation	Abrasive materials

## A. Low-Energy Mills

### 1. Hand Screen

- Size reduction occurs primarily by shear.
- They are made of brass or stainless steel and consist of a woven wire cloth stretched in a circular or rectangular frame.
- They are available in sizes ranging from 4 to 325 mesh; however, for granulation, mesh sizes from 4 to 20 are primarily used.
- They are most widely used for sieve analysis or for size reduction of wet and dry granules in early stages of formulation development.

### 2. Oscillating-Rotary Granulators

- They consist of an oscillating bar contacting a woven wire screen, and the material is forced through the screen by the oscillating-rotary motion of the bar (Fig. 1).
- Size reduction is primarily by shear with some attrition.
- Speed, rotary or oscillatory motion, and screen size are important variables to be considered during the sizing process.

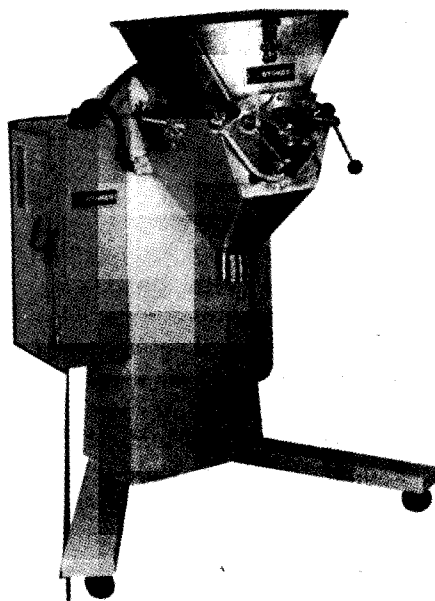


Fig. 1 Oscillating granulator (Stokes Model 43-6).



- They are used exclusively for size reduction of wet and dry granulations and, to some extent, for milling tablets and compacts that must be reprocessed.
- The narrow size distribution and minimum amount of fines are advantages during the size reduction of dry granulation [2].
- Heat-sensitive and waxy materials can be milled owing to the low heat generated during the sizing process.
- Low throughput rates and possible metal contamination from wearing down or broken screen are some of its limitations.

### 3. Extruders

- Primarily used for continuous wet granulation.
- Wet material is forced through a screen and the extruded material is dried in a tray or fluid bed dryer or can be spheronized to produce granules with high degree of sphericity and then dried for controlled-release applications.
- Less dust generation and more uniform granules are some of the advantages.

## B. High-Energy Mills

### 1. Hammer Mill

The hammer mill is one of the most versatile and widely used mills in the pharmaceutical industry. The principle of size reduction in the hammer mill is one of high-velocity impact between rapidly moving hammers mounted on a rotor and the powder particles (Fig. 2 a, b). A wide range of particle sizes, down to micron size, can be produced by these mills. The particle shape, however, is generally sharper and more irregular than that produced by compression methods [5]. The particle size reduction is controlled by the force imparted by the hammers and screen opening.

- They can be used for size reduction of wet or dry granulations and milling of raw materials.
- There is a wide range of interchangeable feed throats and variable feed screw systems are available to optimize the feed rate [12].
- Hammers can rotate horizontally or vertically, based on the rotor configuration and at variable speeds.
- Hammers can be fixed or free-swinging.

## Sizing of Granulation

- Hammers with blunt and knife or sharp edges are used for granules [12].
- Screen openings given in square perforation on the surface.
- Feed rate and dryness are relative to the material.
- Type of hammers, size are important.
- Ease of setup, cleanability to handle a wide range of materials are advantages.
- Heat build-up, screen wear are some of the limitations.

### 2. Conical Screening Mills

- It is effective for size reduction of soft to medium hard materials.
- Comminution characterized by high speed, imparting a high degree of spherical shape.
- The impeller imparts the centrifugal action and up the cone (30°).
- The space between the impeller and the screen.
- The size and shape of the particles, configuration, and distribution.
- Used for difficult-to-mill materials.
- Low heat and low wear with the hammer mill.
- The impeller does not cause breakage and metal contamination with an oscillating screen.
- The dual action of the impeller (oscillating) makes this effective for oscillators [14,15].

reduction of wet and dry gran-  
milling tablets and compacts that

minimum amount of fines are  
on of dry granulation [2].

can be milled owing to the low  
process.

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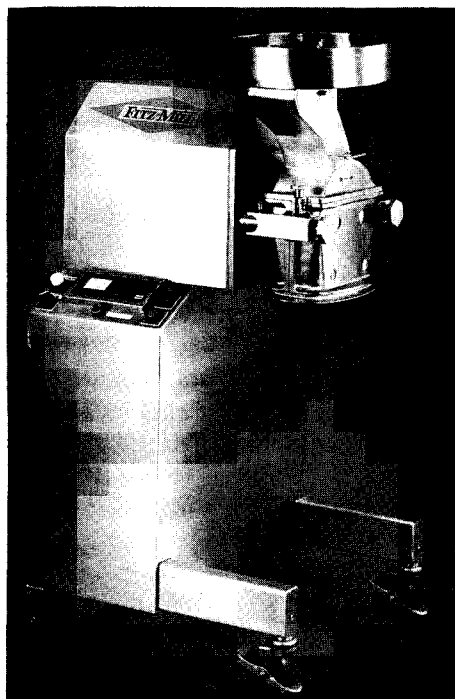
or vertically, based on the rotor  
s.

nging.

- Hammers with blunt or impact edges are preferred for pulverizing, and knife or sharp edges are preferred for chopping or sizing of granules [12].
- Screen openings generally vary from 0.3 to 38 mm, with round or square perforations, diagonal or straight slots, or with a rasping surface.
- Feed rate and dryness of the granules are important variables relative to the material.
- Type of hammers, rotor speed, screen type, thickness, and mesh size are important variables relative to the machine.
- Ease of setup, clean-up, minimum scale-up problems, and ability to handle a wide variety of size and type of feedstock are some advantages.
- Heat build-up, screen wear, and potential clogging of screens are some of the limitations.

## 2. Conical Screening Mill (Comil)

- It is effective for dry (deagglomeration–delumping) and wet mill-  
ing of soft to medium hard materials.
- Comminution chamber consists of an impeller rotating at variable  
speed, imparting a compression or shear force inside a conical-  
shaped screen.
- The impeller imparts a vortex flow pattern to the feed material, and  
the centrifugal acceleration forces the particles to the screen surface  
and up the cone (360°) in a spiraling path [13] (Fig. 3a, b).
- The space between the impeller and the screen can be adjusted.
- The size and shape of the screen holes, screen thickness, impeller  
configuration, and mill speed are important variables.
- Used for difficult-to-mill heat-sensitive material and hard granules.
- Low heat and lower amount of fines are produced when compared  
with the hammer mill; hence, it produces a narrow particle size  
distribution.
- The impeller does not touch the screen; hence, chances of screen  
breakage and metal contamination are greatly reduced compared  
with an oscillating granulator.
- The dual action of conical screening mills (size reduction and mix-  
ing) makes this equipment more desirable than use of traditional  
oscillators [14,15].



(a)



## Sizing of Granulation

### THE FEED THROAT

Introduces material on a tangential path to the comminuting chamber.

### BLADE PROFILE

Helps determine degree of reduction based on material being processed.

### SCREEN TYPE

Helps regulate particle output within a specified size range

### ROTOR SPEED

Works with screen to regulate particle output within the size range

(b)

Fig. 2 Continued

## VI. WET MILLING

The discussion thus far has also be used for wet milling used has larger openings the reasons for wet milling, these

1. To increase surface
2. To improve size un
3. To improve granule
4. To prevent large pa
- ing
5. For further mixing
- mately of the same

As discussed in low she wet granulation method. We such as planetary, ribbon, or combination of high impeller ready for drying. Also, integ milling step is no longer a s

Fig. 2 Hammer mill: (a) Fitzmill model M5A; (b) Principle of operation.

- Integrated designs are available that are attached to a high shear granulator discharge, which provides a deagglomerated lump free product for the dryer (Fig. 4a, b).

### 3. Centrifugal-Impact Mills

Centrifugal-impact mills and sieves are useful to minimize the production of fine particles, because their design combines sieving and milling into a single operation. Unlike the conical-screening mills, these consists of a nonrotating bar or stator that is fixed within a rotating sieve basket. This action produces a very low product agitation and impact; hence, no heat is generated. The particles that are smaller than the hole size of the sieve can pass through the mill without comminution; however, the larger particles are directed by centrifugal force to impact with the stator. Glatt sieve (Fig. 5) and Turbo sieve are examples of this type.

#### THE FEED THROAT

Introduces material on a tangential path to the comminuting chamber.

#### BLADE PROFILE

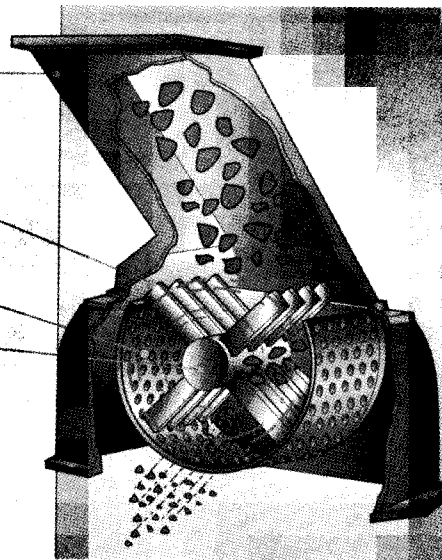
Helps determine degree of reduction based on material being processed

#### SCREEN TYPE

Helps regulate particle output within a specified size range

#### ROTOR SPEED

Works with screen to regulate particle output within the size range



(b)

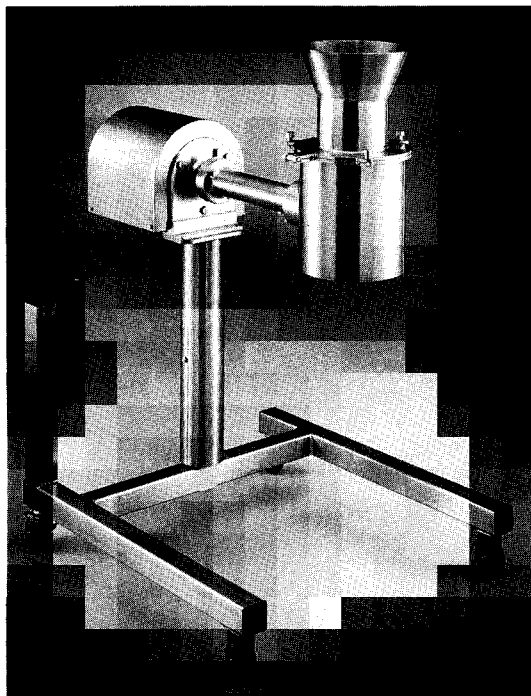
Fig. 2 Continued

## VI. WET MILLING

The discussion thus far has been focused on dry milling. These mills can also be used for wet milling or coarse milling, since the equipment usually used has larger openings than in the dry milling step. There are several reasons for wet milling, these include the following [16]:

1. To increase surface area for more efficient drying
2. To improve size uniformity
3. To improve granule formation
4. To prevent large particles that will shatter to "fines" on dry milling
5. For further mixing or blending because ingredients are approximately of the same size

As discussed in low shear mills, extruders can be used as a continuous wet granulation method. Wet milling is necessary with low shear mixers, such as planetary, ribbon, or sigma mixers, but with high shear mixers, the combination of high impeller speed and built-in choppers produces a product ready for drying. Also, integrated designs are available such that the wet milling step is no longer a separate operation.



(a)

**Fig. 3** Conical-screening mill: (a) Comil model U20; (b) principle of operation.

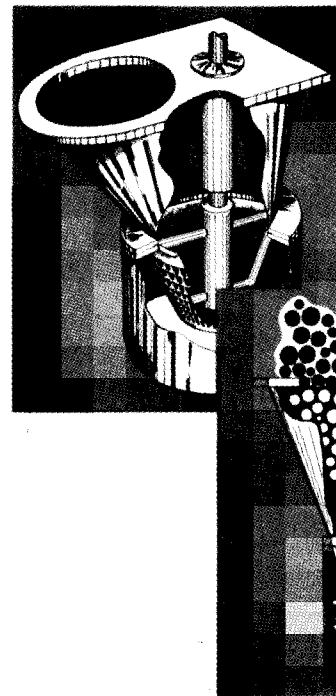
Finally, there are continuous granulators available (M6 NICA granulator) for product applications that do not require extensive kneading treatment and can be used for both batch and continuous operation. The wetted product is discharged in continuous stream through an adjustable opening in the turbine cover. A homogeneous mix is instantly produced in a few minutes, and further milling may not be necessary.

## VII. VARIABLES AFFECTING THE SIZING PROCESS

### A. Process Variables

As discussed in the introduction, the granule properties can dictate the properties of the final tablet. Some of the problems faced during tableting process are flow of granules, maintaining uniform density in the granule bed, and the particle size distribution. Each of the stages of the granulation can be

## Sizing of Granulation



(b)

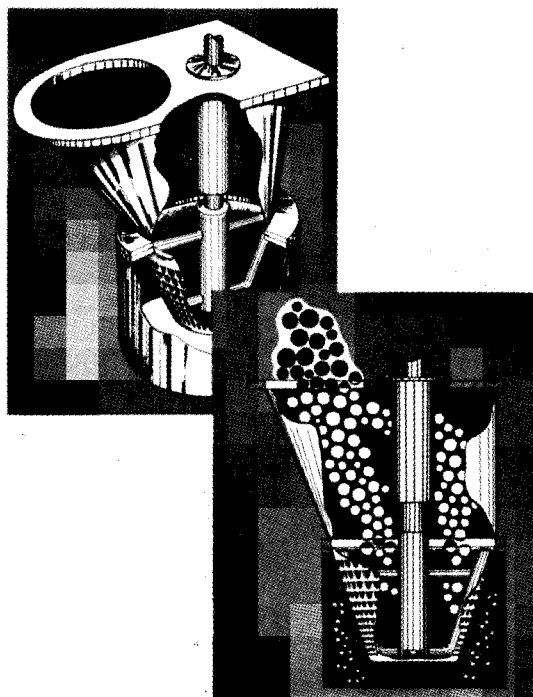
**Fig. 3** Continued

critical and can affect tableting. The sizing process can be controlled along with amount of fines, which influence the packing and density. It depends not only on the properties of the material on the mill and milling parameters, but also because of the excessive heat generated during the final product.

The characteristics of the material on the type of mill; impeller;

### B. Type of Mill

The type of mill chosen can affect the final product. The shape of the milled granules and the mill produces sharp, irregular



(b)

Fig. 3 Continued

U20; (b) principle of operation.

ators available (M6 NICA granu-  
require extensive kneading treat-  
continuous operation. The wetted  
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## SIZING PROCESS

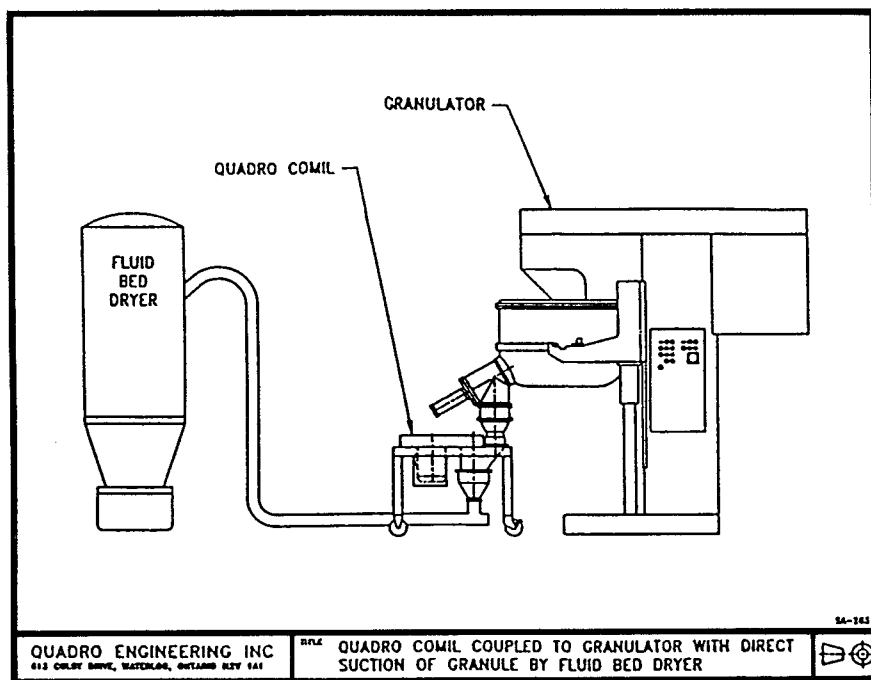
le properties can dictate the prop-  
ems faced during tableting process  
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stages of the granulation can be

critical and can affect tableting. In addition to the wet granulation process, the sizing process can be critical for the particle size distribution which, along with amount of fines, dictates the flow properties. These, in turn, influence the packing and density of the granules. Reproducibility of batches depends not only on the properties of the unmilled dry granules, but also on the mill and milling parameters. Finally, the dry-milling stage is important because of the excessive heat generated that might affect the stability of the final product.

The characteristics of the granules after size reduction depend mainly on the type of mill; impeller type and speed; screen size, and thickness.

## B. Type of Mill

The type of mill chosen can affect the shape of the granules and throughput. The shape of the milled granules can affect the flow properties. An impact mill produces sharp, irregular particles that may not flow readily, whereas



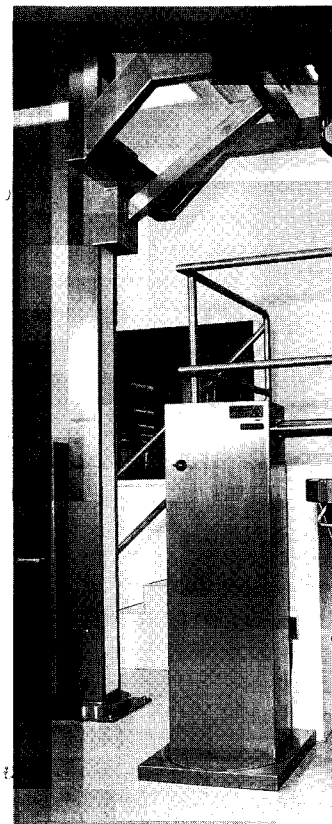
(a)

**Fig. 4** (a) Schematic of an integrated design; (b) an integrated pharmaceutical manufacturing facility.

an attrition mill produces free-flowing spheroidal particles. An oscillating granulator uses shear and attrition as the main mechanisms for size reduction. The granules produced are more spheroidal, as size reduction takes place by surface erosion. If the same material is subjected to impact by hammers in a hammer mill, the granules will shatter and cause irregularly shaped granules. If a conical-screening mill is used for the same material for size reduction, it imparts some shear and some compression between the rotating impeller and the screen.

### 1. Hammer Mill

There are several variables in a hammer mill that can influence comminution [12,17–19]. The following section discusses five operating variables in detail:

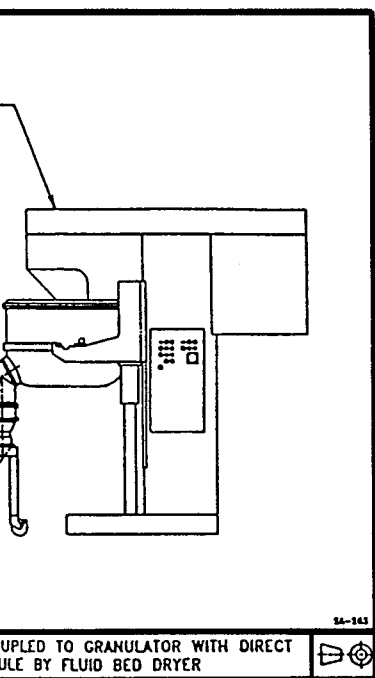


(b)

**Fig. 4** Continued

#### *a. Rotor Shaft Config*

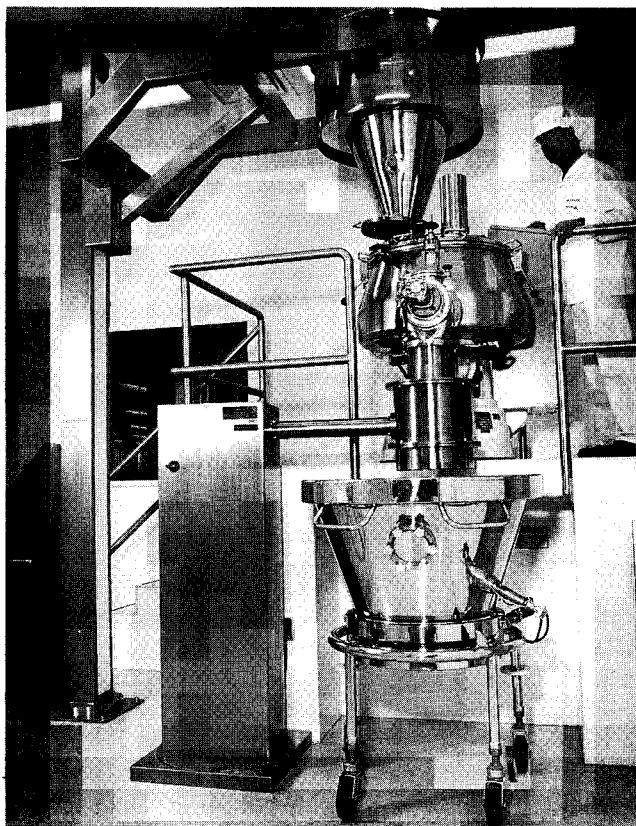
vertical or horizontal shaft (mill) have feed inlets at the swing of the hammers. When the material is fed into the mill (Fitzmill), the material is fed into the mill. The rotor configuration can influence the material flow. In a vertical configuration, the screen provides more open screen area for the material to pass through the milling chamber when com-



gn; (b) an integrated pharmaceutical

heroidal particles. An oscillating  
main mechanisms for size reduc-  
heroidal, as size reduction takes  
material is subjected to impact by  
will shatter and cause irregularly  
mill is used for the same material  
and some compression between the

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asses five operating variables in



(b)

Fig. 4 Continued

*a. Rotor Shaft Configuration.* The hammers may be mounted on a vertical or horizontal shaft (Fig. 6). The vertical shaft mills (Stokes-Tornado mill) have feed inlets at the top and material is fed perpendicular to the swing of the hammers. Whereas, in the case of horizontal shaft (Fitzpatrick-Fitzmill), the material is fed tangentially to the hammer swing. Rotor configuration can influence the particle size distribution of granules. In the vertical configuration, the screen is placed 360° around the hammers, and this provides more open screen area and less time for the granules to stay in the milling chamber when compared with the horizontal shaft mills.



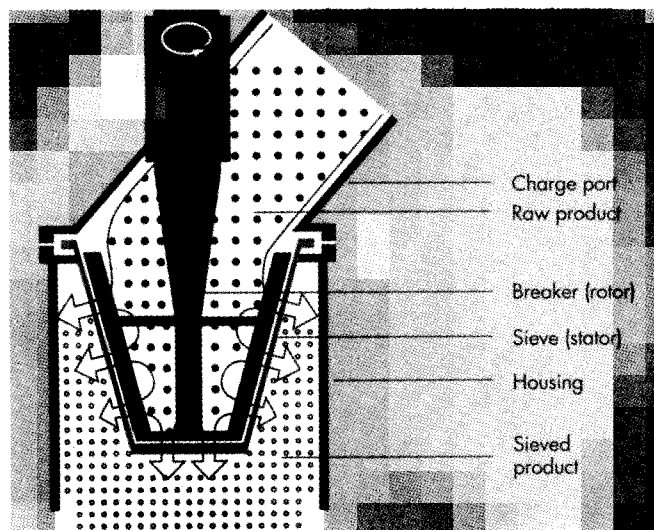


Fig. 5 Principle of operation (Glatt Sieve).

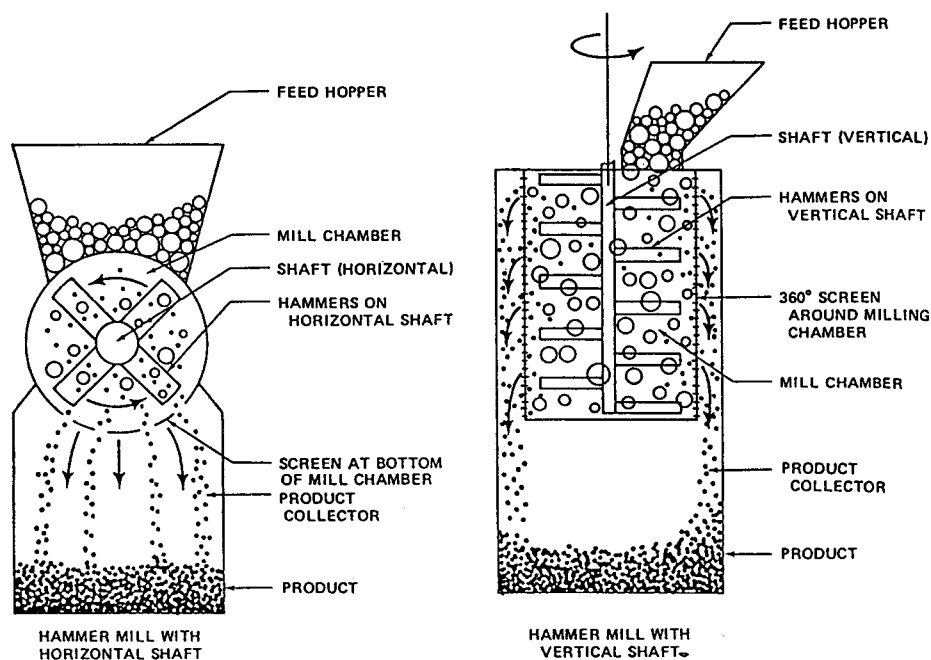
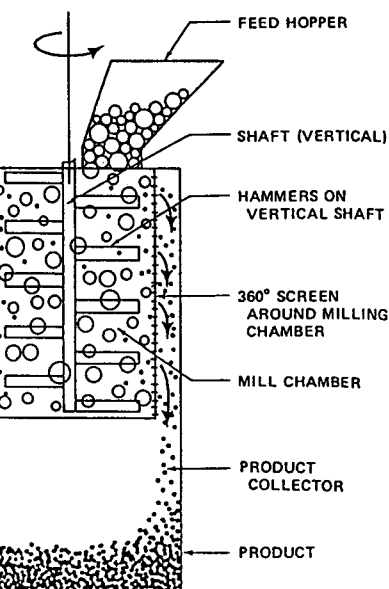
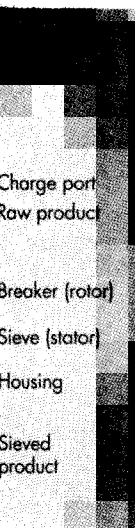


Fig. 6 Different types of hammer mills.

**b. Material Feed Rate.** The material that enters the mill must be underfeeding (starving) the mill. The particle size distribution, overloading of feed is relatively slow, the rate of undersized material or material stays in the milling chamber is impeded by the mass of material. The rule of thumb is to keep the feed rate low. The feed rate can be controlled by feeders, or dischargers controlling the flow, the feed throat must be large enough. There are more than 50 feed throats for optimizing the milling operations are designed so that the discharge, generally from the

**c. Blade Type.** Compared with the fast-moving blades of a hammer mill, the blades of a hammer mill have a knife edge on the other side. Many types of blades to use. Many types of blades can be turned 180°, so that the knife edge can be used for grinding surface and the impact during grinding. The knife edge, because of the impact, thereby generating larger granules. The blades are reversible—are installed in pairs. The blades plough through the material and lay back and depend on the material. They are easier to clean and work at higher speeds, or when grinding fine material is needed. The material to be ground is on the blades on the motor shaft, the blades (straight, stepped, stepped, etc.) are a preference; little empirical data is available on the shape over another. The size of the blades, the number of blades (e.g.,

**d. Rotor Speed.** The speed of the hammers. As the speed of the hammers, maintaining constant, the faster

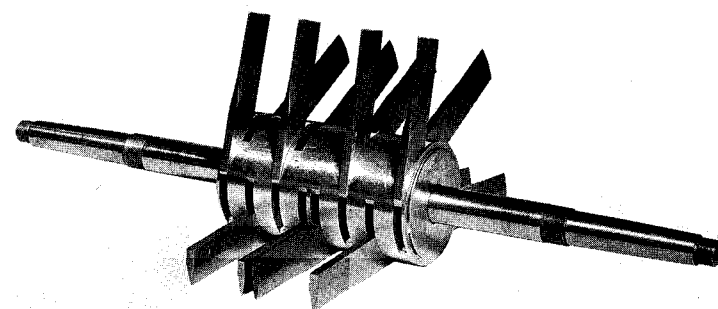


HAMMER MILL WITH VERTICAL SHAFT

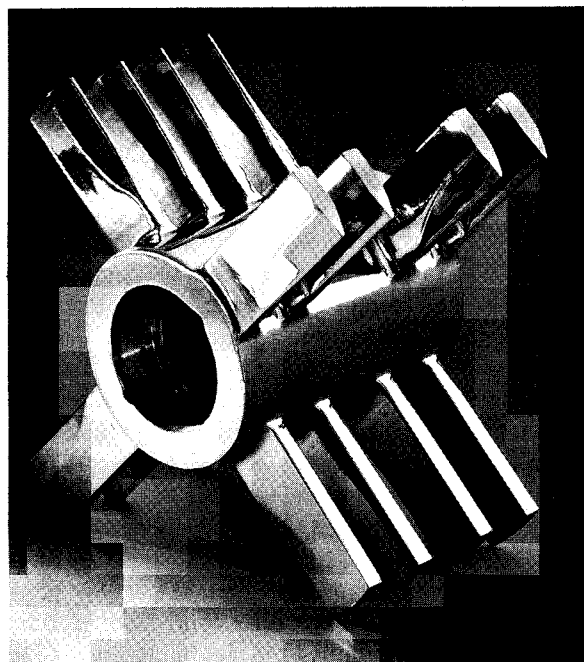
*b. Material Feed Rate.* The feed rate controls the amount of the feed material that enters the comminutor and prevents overfeeding (slugging) or underfeeding (starving) the milling chamber. Although both affect the particle size distribution, overfeeding is relatively more detrimental. If the rate of feed is relatively slow, the product is discharged readily, and the amount of undersized material or fines is minimized. On the other hand, overfed material stays in the milling chamber for a longer time, because its discharge is impeded by the mass of material. This leads to a greater reduction of particle size, overloads the motor, and the capacity of the mill is reduced. The rule of thumb is to keep the feed rate equal to the rate of discharge. The feed rate can be controlled by using variable-feed screws, vibratory feeders, or dischargers controlled by gravity. In addition to controlling the flow, the feed throat must allow the material to enter at a proper angle. There are more than 50 feed throat designs available that one needs to consider for optimizing the milling process. Most mills used in the pharmaceutical operations are designed so that the force of gravity is sufficient to give free discharge, generally from the bottom of the mill.

*c. Blade Type.* Comminution is effected by impact of the material with the fast-moving blades and attrition with the screen. Generally, the blades of a hammer mill have a blunt or flat edge on one side and a sharp or knife edge on the other side. The desired particle size range determines which blades to use. Many models of hammer mills have a rotor that may be turned 180°, so that the blunt edges can be used for fine grinding, or the knife edge can be used for cutting or granulating. The blunt edge offers the surface and the impact during the milling, generating smaller granules. The knife edge, because of the sharper edge, causes cutting of the granules, thereby generating larger granules. Individual blades—whether blunt, sharp, or reversible—are installed either fixed or swinging (Fig. 7 a, b). Fixed blades plough through the material being ground, whereas swinging blades lay back and depend on the centrifugal force for movement. Fixed blades are easier to clean and work better than the swinging blades at low rotor speeds, or when grinding fibrous material, or if carefully controlled grinding is needed. The material to be ground determines the configuration of the blades on the motor shaft, as well as the blade density. The shape of the blades (straight, stepped, sickle, or other) is largely a matter of designer preference; little empirical evidence exists to establish the superiority of one shape over another. The size of the grinding chamber generally determines the number of blades (e.g., a 6-in. grinding chamber will have 16 blades).

*d. Rotor Speed.* The size of a product is markedly affected by the speed of the hammers. As a general rule, and with all other variables remaining constant, the faster the rotor speed, the finer the grind. Usually,



(a)



(b)

Fig. 7 Rotor configurations—Fitzmill: (a) swinging rotor; (b) fixed rotor.

## Sizing of Granulation

three speed settings are available: slow (1000 rpm), medium (2500 rpm), and fast (4000 rpm). Changeover is by electric speed drive or by manually operated gear ratio. Rotor speeds of 2500 rpm are used in fine grinding applications. The mill is usually used with knife edges. The blades are wider at low speed than at high speed. At critical rotor speed, material is ground more spheroidally, which causes more spheroidal material.

### e. Screen Size and Type

the hammer mill, and does not depend on the hole opening of the screen. The speed of the hammer is much smaller than the size of the particle with high particle velocity.

Screens can be performed in various configurations. Because of the nature of the perforated screens are used if the raw material fuses from the mill, woven-type screens are used. The herringbone design and cross-hatch design are used for crystalline materials (Fig. 8).

## 2. Conical-Screening Mill

Similarly, for conical-screening mills, the size distribution are, type of material, and type.

### a. Impeller. There are

9); however, the four main types are:

- 1607: Knife edge, pressure is used for compression.
- 1601: Round edge, pressure throughput, low deagglomeration—compression.
- 1611: Same as 1601, throughput, reduced breaking with teeth, rework.

three speed settings are available: slow (1000 rpm), medium (2500 rpm), and fast (4000 rpm). Changes in rotor speed are accomplished by variable-speed drive or by manually changing the hammer drive and motor pulley ratio. Rotor speeds of 2500–4000 rpm are typically used with blunt edges in fine grinding applications, whereas speeds of 1000–2500 rpm are typically used with knife edges for coarse grinding. Particle size distributions are wider at low speed than at medium and high speeds [12]. Below the critical rotor speed, material experiences attrition, rather than impact action, which causes more spheroidal granules and may result in overheating of the material.

*e. Screen Size and Type.* The screen is usually the integral part of the hammer mill, and does not act as a sieve. The particle size of the product depends on the hole opening in the screen, the thickness of the screen, and the speed of the hammer. The particle size of the output granules will be much smaller than the size of the screen used, because they exit at an angle, with high particle velocity.

Screens can be perforated, woven wire type, or with a slot configuration. The screen openings may range in size and open area, based on screen configuration. Because of the large forces that the screens are subjected to, the perforated screens are preferred over the woven-type screens. However, if the raw material fuses from the heat generated, or if the material is difficult to mill, woven-type screens are preferred for their increased open area. The herringbone design and cross-slot are preferred for grinding amorphous and crystalline materials (Fig. 8).

## 2. Conical-Screening Mill (Comil)

Similarly, for conical-screening mills, the operating variables affecting particle size distribution are, type of impeller, impeller speed, and screen size and type.

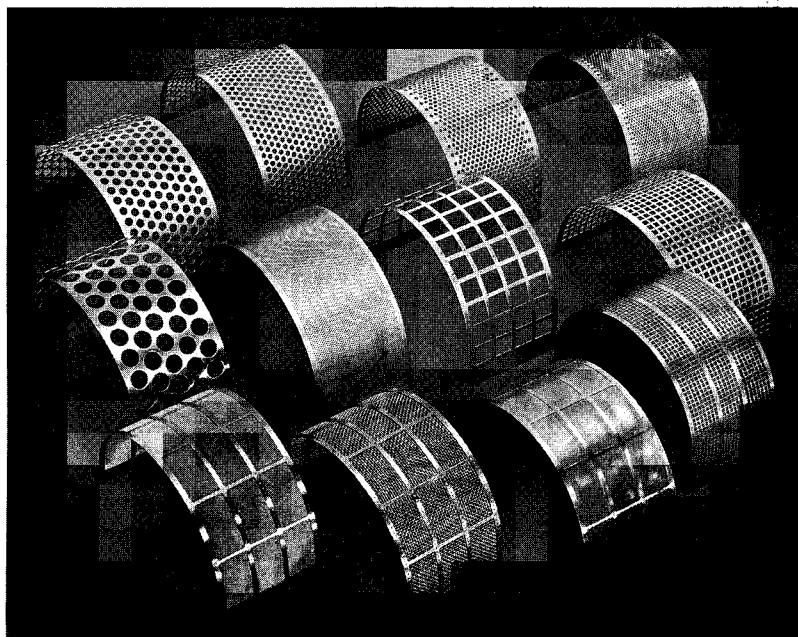
*a. Impeller.* There are several types of impellers available [13] (Fig. 9); however, the four main types used frequently are:

1607: Knife edge, principal mode of operation is shear and, hence, it is used for compression-sensitive, heat-sensitive materials.

1601: Round edge, principal mode of operation is compression, high throughput, low retention; it is mainly used for wet or dry deagglomeration–delumping.

1611: Same as 1601, but has teeth on one side, aggressive, high throughput, reduces fines in milling compacted materials by pre-breaking with teeth and reducing retention time; it is used for tablet rework.

ing rotor; (b) fixed rotor.



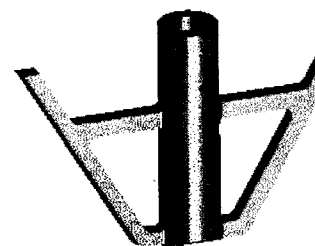
**Fig. 8** Different types of Fitzmill screens.

1901: Knife edge, low-intensity impeller, used when a shear or cut is required; it gives a scissor-like action, for fibrous materials or capsule rework.

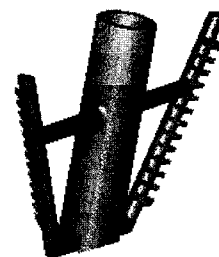
*b. Speed.* The speed of the impeller can affect the particle size of the product. Comils available have variable or fixed speed drives, however, rpms vary depending on the size of the impeller. It is suggested that one keep the tip speed of the impeller the same on scale-up to achieve the same particle size distribution.

*c. Screen Size and Type.* Screens are available in various sizes, based on thickness, open area, and hole configuration, such as round, square, slotted, and grater-type openings. Only perforated screens are available.

The effects of these mill variables on granulation-milling process has been extensively studied by various researchers [20–22]. Motzi et al. [21], based on their observations of significant interaction effects, concluded that effects of mill speed, screen size, and impeller shape on particle size distribution, cannot be evaluated individually, but must be evaluated at a level which is a combination of all three.

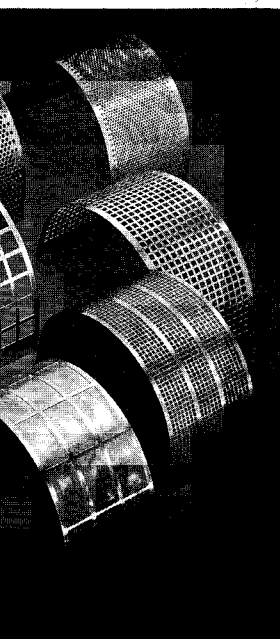


MODEL : 1607



MODEL : 1611

**Fig. 9** Various types of Comil impellers.

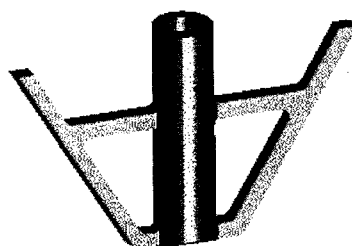


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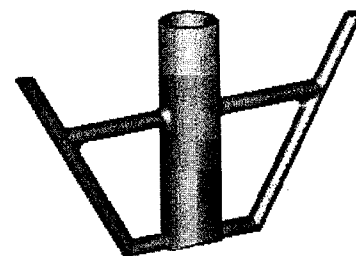
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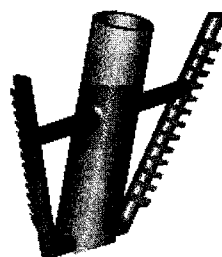
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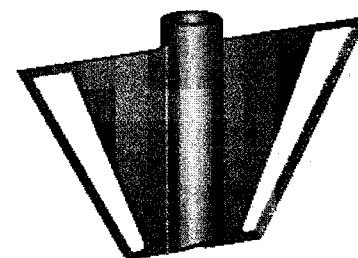
MODEL : 1607



MODEL : 1601



MODEL : 1611



MODEL : 1901

Fig. 9 Various types of Comil impellers.

### C. Other Variables

There are other variables that can affect the sizing process, such as feed material properties, granulation process, and drying process. The properties of materials have been discussed in Section III. The type of granulation (i.e., dry [roller compaction], planetary, high shear, or fluid bed) can determine the strength of the granules and, hence, the sizing process. Furthermore, the drying process, whether tray or fluid bed, can also be important. Tray-dried granules are usually case-hardened and difficult to mill, whereas the fluid bed process yields more porous and friable granules. Similarly, granules produced by high shear granulators are harder; therefore, they are more difficult to mill than those manufactured using low shear or fluid bed processes.

## VIII. SCALE-UP

### A. Hammer Mill

Table 2 shows various sizes of Fitzmills available [12]. In addition to having the same screen size and type used on the lower scale, keeping the speed of the rotor constant is one of the most important considerations in scale-up of a milling process. Vertical and horizontal rotor configurations may affect throughput and also particle size distribution.

### B. Comil

Table 3 shows the scale-up parameters for various Comils [13]. In addition to having the same impeller type, screen size, and screen type used on the lower scale, the tip speed of the impeller is one of the key variables in scale-up; thus it should be kept constant.

## IX. CASE STUDIES

### A. Comparison of Fitzmill Versus Comil

It is often difficult to predict the results from similar pieces of equipment having the same operating principle at two different scales, let alone using two pieces of equipment having different operating principles. Many times in the development of a pharmaceutical dosage form the equipment used during formulation development and that used in production is quite different. Apelian et al. [22] studied the effect on particle size distribution of chlorpheniramine maleate granules using a Fitzmill and Comil. For the Fitz-

Table 2 Scale-up Parameters for Fitzmill

Rotor

Chamber

the sizing process, such as feed and drying process. The properties of the granules (i.e., size, shape, or fluid bed) can determine the sizing process. Furthermore, the properties of the granules can also be important. Tray-dried granules are difficult to mill, whereas the fluid bed granules are easy to mill. Similarly, granules that are hard to mill; therefore, they are more difficult to mill using low shear or fluid bed

available [12]. In addition to having a lower scale, keeping the speed of the granulation is an important consideration in scale-up. Horizontal rotor configurations may be used for scale-up.

various Comils [13]. In addition to the size, and screen type used on the mill, one of the key variables in scale-

mill. From similar pieces of equipment at different scales, let alone using different operating principles. Many times the equipment used in production is quiet different from the equipment used in production. For the Fitz-

Table 2 Scale-up Parameters for Fitzmill

Model	Chamber				Rotor			
	Capacity <sup>a</sup> factor	Nominal width	Screen area (in. <sup>2</sup> )	Diameter of chamber	Rotor configuration	No. of blades	Tip speed factor <sup>b</sup>	Maximum rpm horsepower
Homoloid	0.4×	2.5	43.0	6.625	Horizontal	12	1.73	7200 10.0
M5A	0.7×	4.5	76.0	8.0	Horizontal	16	2.09	4600 3.0
D6A	1.0×	6.0	109.0	10.5	Horizontal	16	2.75	4600 5.0
DAS06	1.0×	6.0	109.0	10.5	Horizontal	16	2.75	4600 15.0

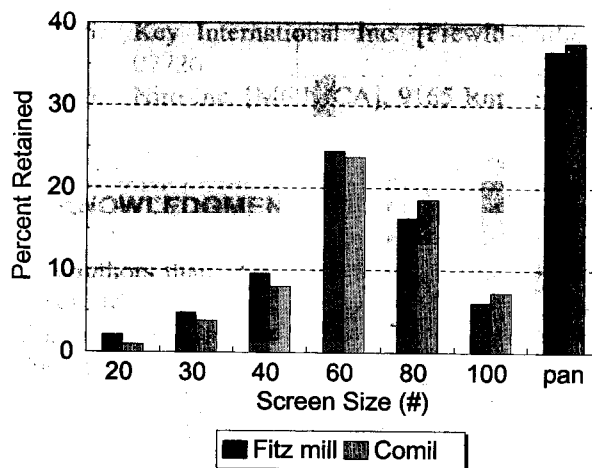
<sup>a</sup>Throughput relative to Model D6 at same tip speed.

<sup>b</sup>Tip speed = factor × operating speed.

Source: Ref. 12.





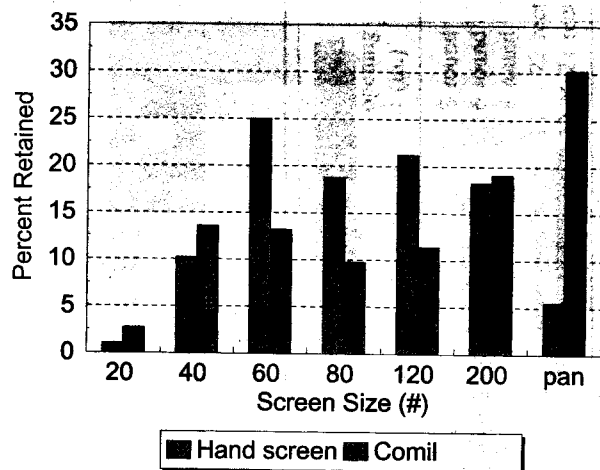


**Fig. 10** Particle size distribution of chlorpheniramine maleate granulations milled using Fitzmill and Comil.

mill, various screens sizes (1, 2, 3, and so on) at medium speed were evaluated, and for the Comil, impellers (1601 and 1607) at two speeds (1680 and 3420 rpm) using various screen sizes (039, 045, 055, and 055G) were studied. They reported that milling the granulation using a Fitzmill, with a screen size of 2, at medium speed gave a particle size distribution similar to the granulation milled using a Comil (1601 impeller, 055 screen at 1680 rpm) (Fig. 10). The results of this study suggest that in making a major change in the milling process one needs to optimize the critical-processing variables to achieve a similar particle size distribution.

### B. Comparison of Hand Screen versus Comil

The effect of changing the dry milling from a hand screen operation to a Comil is shown in Fig. 11. Naproxen granulations (0.5 and 4 kg) were manufactured in a fluid bed granulator using PVP K-90 as a binder [23]. Particle size distribution of granules (0.5 kg), passed manually through an 18-mesh screen, was much coarser than the granules (4 kg) that were milled using a Comil (Model 197S). A flat-faced impeller (1607) at an impeller speed of 2500 rpm, with a spacer setting 0.25 in., and screen number 2A055 (14 mesh) were used for the milling operation. Even though the granulations were prepared by the same procedure, the milling conditions drastically affected the particle size distribution. As a general rule, during a switchover from the low-energy milling operation to a high-energy milling operation,



**Fig. 11** Particle size distribution of naproxen granulations milled using hand screen and Comil.

the screen size should be coarser in the high-energy mill. The particle velocity is higher and, therefore, the size of the granule exiting out of the screen is much smaller than the screen opening. As seen from Fig. 11, when the screen size was increased to 14 mesh for the cone mill, the amount of fines generated was higher in the cone mill. Hence, during scale-up, optimization of milling conditions may be necessary to achieve the same particle size distribution.

## X. LIST OF EQUIPMENT SUPPLIERS

- Oscillating granulators
  - DT Industries Packaging Group, Stokes Division, 1500 Grundy's Lane, Bristol, PA 19007
  - Vector Corporation [Colton], 675 44th Street, Marion, IA 52302
  - Key International Inc. [Frewitt], 480 Route 9, Englishtown, NJ 07726
- The Fitzmill Company [Fitzmill], 832 Industrial Drive, Elmhurst, IL 60126
- Quadro Inc. [Comil], 55 Bleeker Street, Millburn, NJ 07041
- Glatt Air Techniques Inc. [Glatt Sieve], 20 Spear Road, Ramsey, NJ 07446

## Sizing of Granulation

- Key International 07726
- Niro Inc. [M6 NICA]

## ACKNOWLEDGMENTS

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## REFERENCES

- JK Prescott, RJ Hossfeld. Flow to direct-compression technology. *Pharmaceutical Dosage Forms*, 1990, pp. 107-157.
- RJ Lantz Jr. Size reduction. *Pharmaceutical Dosage Forms*, 1990, pp. 107-157.
- DE Fonner, NR Anderson, In: HA Lieberman, L Lachman, Vol 2. New York: Marcel Dekker, 1980, pp. 21-46.
- EL Parrot. Milling. In: L Lachman, and Practice of Industrial Pharmacy, 21-46.
- RE O'Connor, ED Rippie. Remington's Pharmaceutical Chemistry, 1615-1617.
- JT Carstensen, F Puisieux, *Int J Pharm* 1:65-70, 1978.
- G Steiner, M Patel, JT Carstensen. Size distribution. *J Pharm Sci*, 1984, 73:928, 1984.
- JJ Motzi, NR Anderson. The process. III. Prediction of particle size. *J Pharm Sci*, 1984, 73:928, 1984.
- RH Snow, BH Kaye, CE Cramer. In: RH Perry, D Greninger, New York: McGraw-Hill, 1950, pp. 1-10.
- MH Prior, H Prem, MJ Rhoten. *of Powder Technology*. New York: Wiley, 1978, pp. 1-10.



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Sieve], 20 Spear Road, Ramsey,

5. Key International Inc. [Frewitt-Turbo Sieve], Englishtown, NJ 07726
6. Niro Inc. [M6 NICA], 9165 Rumsey Road, Columbia, MD 21045

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## REFERENCES

1. JK Prescott, RJ Hossfeld. Maintaining product uniformity and uninterrupted flow to direct-compression tableting presses. *Pharm Technol* 18:98-114, 1994.
2. RJ Lantz Jr. Size reduction. In: HA Lieberman, L Lachman, JB Schwartz, eds. *Pharmaceutical Dosage Forms: Tablets, Vol 2*. New York: Marcel Dekker, 1990, pp. 107-157.
3. DE Fonner, NR Anderson, GS Banker. Granulation and tablet characteristics. In: HA Lieberman, L Lachman, eds. *Pharmaceutical Dosage Forms: Tablets, Vol 2*. New York: Marcel Dekker, 1981, p. 201.
4. EL Parrot. Milling. In: L Lachman, HA Lieberman, JL Kanig, eds. *The Theory and Practice of Industrial Pharmacy*. Philadelphia: Lea & Febiger, 1986, pp. 21-46.
5. RE O'Conner, ED Rippie, JB Schwartz. Powders. In: AR Gennaro, ed. *Remington's Pharmaceutical Sciences*. Easton: Mack Publishing, 1990, pp. 1615-1617.
6. JT Carstensen, F Puisieux, A Mehta, MA Zoglio. Milling kinetics of granules. *Int J Pharm* 1:65-70, 1978.
7. G Steiner, M Patel, JT Carstensen. Effect of milling on granulation particle-size distribution. *J Pharm Sci* 63:1395-1398, 1974.
8. JJ Motzi, NR Anderson. The quantitative evaluation of a granulation milling process. III. Prediction of output particle size. *Drug Dev Ind Pharm* 10:915-928, 1984.
9. RH Snow, BH Kaye, CE Capes, GC Sresty. Size reduction and size enlargement. In: RH Perry, D Green, eds. *Perry's Chemical Engineers' Handbook*. New York: McGraw-Hill, 1984, pp. 8-9-8-20.
10. MH Prior, H Prem, MJ Rhodes. Size reduction. In: MJ Rhodes, ed. *Principles of Powder Technology*. New York: John Wiley & Sons, 1990, pp. 237-240.

11. RJ Kukla. Strategies for processing heat-sensitive materials. *Powder Bulk Eng* 2:35-43, 1988.
12. Fitzmill Technical Bulletin, The Fitzpatrick Company, Elmhurst, IL.
13. Comil Product Literature, Quadro Inc., Millburn, NJ.
14. RP Poska, TR Hill, JW van Schaik. The use of statistical indices to gauge the mixing efficiency of a conical screening mill. *Pharm Res* 10:1248-1251, 1993.
15. GL Fourman, DL Cunningham, L Gerteisen, JF Glasscock, RP Poska. Improved color uniformity in tablets made by the direct compression method: a case study. *Pharm Technol* 14:334-44, 1990.
16. JB Schwartz. Theory of granulation. In: KL Kadam, ed. *Granulation Technology for Bioproducts*. Boca Raton: CRC Pres, 1990, p. 17.
17. C Johnson. Comminution variables and options. *Powder Bulk Eng* 3:40-44, 1989.
18. JM Owens. How to correct common hammermill problems. *Powder Bulk Eng* 5:38-43, 1991.
19. BR Hajratwala. Particle size reduction by a hammer mill I: Effect of output screen size, feed particle size, mill speed. *J Pharm Sci* 71:188-190, 1982.
20. JE Byers, GE Peck. The effect of mill variables on a granulation milling process. *Drug Dev Ind Pharm* 16:1761-1779, 1990.
21. JJ Motzi, NR Anderson. The quantitative evaluation of a granulation milling process. II. Effect of output, screen size, mill speed and impeller shape. *Drug Dev Ind Pharm* 10:713-728, 1984.
22. V Apelian, M Yelvigi, GH Zhang, et al. Comparison of Quadromill and Fitzmill used in milling process of granulation. *Pharm Res* 11:S-142, 1994.
23. LL Augsburgberger et al. An approach toward establishing a scientific foundation for interpreting regulations and workshop reports on scale-up and post-approval changes. *Pharm Res* 11:5143, 1994.

# 14

## Granulation C Methods and

**Christopher M. Sinko**  
*Pfizer, Inc., Groton, Conne*

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- II. MATERIAL PROPE
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  - C. Fluid Bed Gran
  - D. Dry Granulation
  - E. Characterization
- IV. SUMMARY
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Pharm Res 10:1248-1251, 1993.

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the direct compression method: a

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# 14

## Granulation Characterization: Methods and Significance

**Christopher M. Sinko**

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## I. INTRODUCTION

Dosage form performance is assessed through a characterization program in which bioavailability, chemical stability, or manufacturing ruggedness is taken into account. The selection of excipients and manufacturing processes are based on some expectation of the performance of the dosage form, whether it is physical or chemical. A decision to granulate is made when, after initial characterization, the formulation does not meet the scientist's expectation for specific volume, flowability, compressibility, content uniformity, or other properties. The scientist can rely on many different tools for dosage form characterization. These tools can probe the molecular, particulate, and bulk or macroscopic attributes of material. In this chapter many characterization techniques that are applied to granulation will be reviewed.

This chapter is split into two major parts. The first serves as a review of properties and the most common techniques that are used to measure these properties. The second part covers the application of some of these techniques to granulation development in general: the selection of composition or process, process development, and process scale-up. The examples in this second part are drawn from the literature which covers low shear, high shear, fluid bed, and dry granulation.

## II. MATERIAL PROPERTIES AND TECHNIQUES

Many of the characterization reports in the literature that pertain to pharmaceutical granulations have extensive descriptions of physical property characterization. Chemical properties are equally important because of the expectations, or more precisely, specifications of a dosage form cover content uniformity, chemical purity, and in vitro performance. The interaction between the physical characteristics of a formulation and chemical-based performance should not be understated. Ultimately, in vivo performance such as bioequivalence is the ultimate performance test because it is this "characterization" that ultimately determines whether a pivotal bioequivalency batch passes or fails. The effect of granule size on the dissolution performance, for example, could ultimately affect the outcome of such a bioequivalence study. The complexity of this kind of relation underscores how something seemingly simple, such as particle size and its dependence on granulation process parameters, can influence dissolution and ultimately in vivo performance.

Physical characterization can be completed at the molecular, particulate, or bulk (macroscopic) level [1]. From the terminology cited by Brittain et al., *molecular properties* are associated with individual molecules, *particulate*

*ulate properties* are considered for particles," and *bulk properties* are associated with the bulk of particulate species [1]. Molecular properties are associated with physical characterization, and particulate properties are associated with bulk level or macroscopic characterization. Bulk properties could be considered as either molecular or particulate level, but in this section particulate level characterization is emphasized.

### A. Particulate Level Characterization

#### 1. Particle Morphology

Particle morphology can be characterized in many ways. Examples can be taken directly from the literature, such as the use of a microscope or sorted using a laser light scattering technique, which the granulation is fed into a classifier which separates particles of different shape and size. The most common analysis by microscopy.

Shape can be quantified in many ways. One method is through the use of a shape factor. The *shape coefficient* is defined as the ratio of the surface area of a sphere to the volume shape factor. The shape coefficient for a sphere would be 1.0, its projected area in its maximum cross-section [2]. Cutting the cube in half increases the surface area to 9.0, whereas it increases to 1.0 for a sphere. Further details are given by Rupp [2].

The effect of particle shape on flow is illustrated by Rupp [2]. The effect of particle density and flow rate is illustrated by these examples, packing of particles. The effect of the shape factor or loss in sphericity is worse with loss in sphericity.

#### 2. Particle Size Distribution

Particle size distribution can be characterized by scattering, or optical microscopy. Scattering is generally not applied to granulation. Dry sieve analysis and microscopy are the most common methods for characterizing

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*ulate properties* are considered properties that pertain to "individual solid particles," and *bulk properties* are those that are associated with an assembly of particulate species [1]. Most reports in the pharmaceutical literature cover physical characterization, and most of these articles could be considered to be bulk level or macroscopic properties. The assembly of particulate species could be considered as either the granulation itself, or the tablet form. In this section particulate level characterization is treated separately from bulk level characterization.

### A. Particulate Level Characterization of Granulations

#### 1. Particle Morphology

Particle morphology can be assessed through optical microscopy [2]. Samples can be taken directly from the granulation and evaluated under a microscope or sorted using a device proposed by Ridgway and Rupp [3] in which the granulation is fed onto a triangular metal deck and vibrated. Particles of different shape will segregate on this deck and be collected for analysis by microscopy.

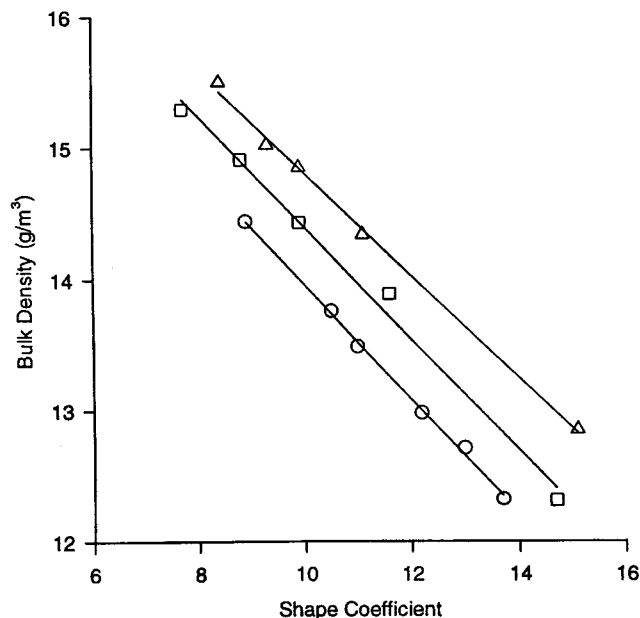
Shape can be quantified by many different methods. One popular method is through the use of Heywood coefficients [2]. The *Heywood shape coefficient* is defined as the ratio of the surface shape coefficient ( $\pi$  for a sphere) to the volume shape coefficient ( $\pi/6$  for a sphere); hence, the shape coefficient for a sphere would be 6.0 [2]. Applying this to a cube and using its projected area in its most stable position, the shape coefficient is 6.8 [2]. Cutting the cube in half in one dimension increases the shape factor to 9.0, whereas it increases to 26.6 if that cube was sliced one-tenth in one dimension [2]. Further details of these types of calculations are provided by Rupp [2].

The effect of particle shape on bulk powder properties has also been illustrated by Rupp [2]. The effect of particle size and shape on the bulk density and flow rate is illustrated in Figs. 1 and 2 [2]. As illustrated in these examples, packing of powder in the bulk becomes more efficient as the shape factor or loss in sphericity increases. The flow rate also becomes worse with loss in sphericity.

#### 2. Particle Size Distribution

Particle size distribution can be measured using sieve analysis, laser light scattering, or optical microscopy [1]. Light-scattering techniques are generally not applied to granulations owing to the large size of the granules; dry sieve analysis and microscopic techniques are generally the most popular methods for characterizing the size distribution of granules. Microscopic



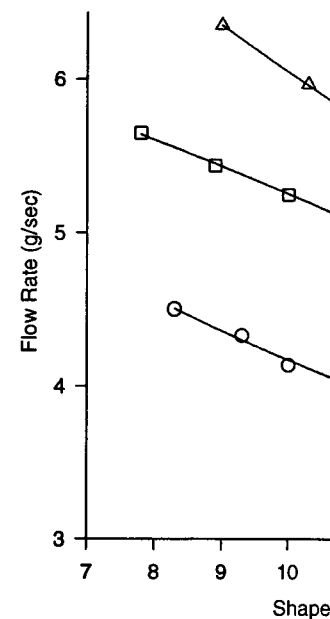


**Fig. 1** Bulk density as a function of shape factor: triangles, 302  $\mu\text{m}$ ; squares, 461  $\mu\text{m}$ ; circles, 805  $\mu\text{m}$ . (From Ref. 3.)

techniques are probably the most exact measurement of size, although it is also the most labor-intensive method. Computer-aided image analysis techniques have been employed to simplify the method, but some problems, such as three-dimensional surface effects could be misinterpreted by the computer, resulting in errors in the calculated distribution.

Dry sieve analysis is the easiest and most convenient method for measuring granule size. The granulation is placed on top of a stack of five to six sieves which have successively smaller-sized openings from top to bottom. The stack is vibrated, and the particles are collected on the surface of each sieve. The data is usually represented in terms of percentage retained on the sieve, or percentage that is undersize or oversize versus screen-opening size (Fig. 3).

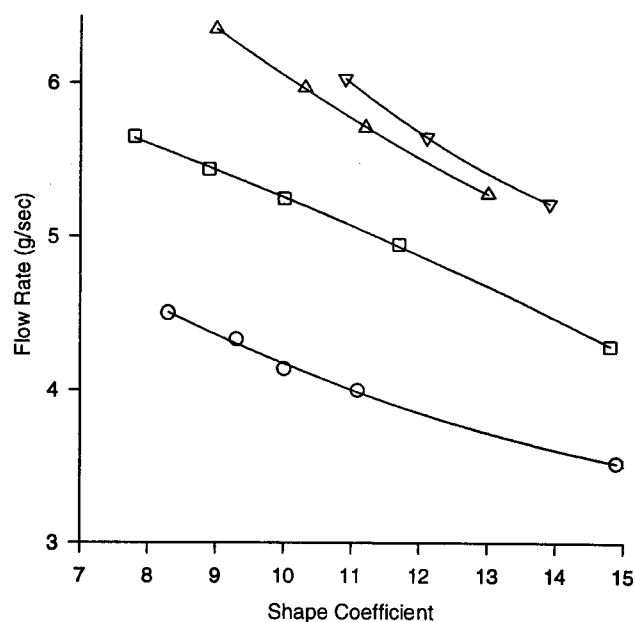
Two factors—particle size distribution and shape—can bias a distribution obtained by sieve analysis. Shergold attributes the cause of variations in distribution to the loading of the stack which, in turn, is affected by the particle size distribution and shape of the powder being analyzed [4]. In a more extensive evaluation Fonner and co-workers studied the effect of loading, shaker speed, and time on the data obtained for the particle size distribution.



**Fig. 2** Effect of particle shape on flow rate: triangles, 302  $\mu\text{m}$ ; squares, 461  $\mu\text{m}$ ; circles, 805  $\mu\text{m}$ .

tribution of model granulation shaker speeds and times. Ac material influences the time the time at which the material particle attrition [5]. The aut of particle size distribution for each sieve [5].

An example of the use addressed the effect of gran tablets by constructing “iso uation was to define a geom result in an acceptable table viation was inverted and na mean diameters and distrib and running on a rotary tab the tablet weight was recor geometric mean diameter we on a contour plot containing



**Fig. 2** Effect of particle shape on flow rate for an orifice diameter of 6.34 mm: triangles, 302  $\mu\text{m}$ ; squares, 461  $\mu\text{m}$ ; circles, 805  $\mu\text{m}$ . (From Ref. 3.)

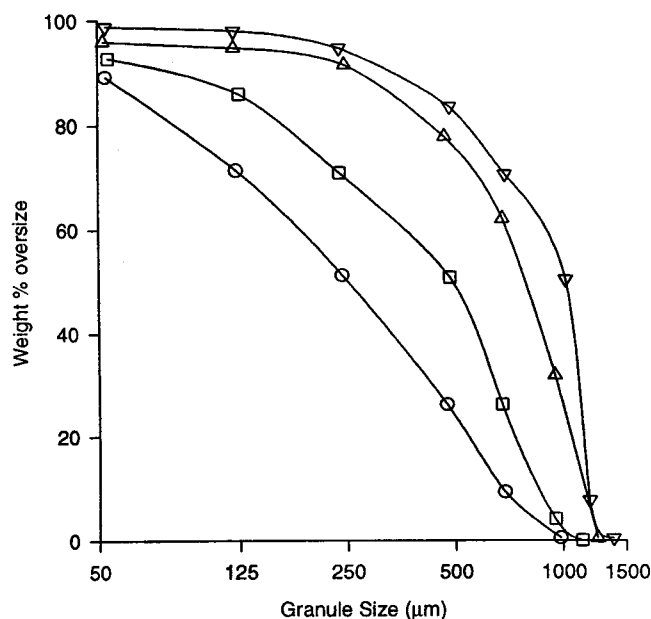
measurement of size, although it is computer-aided image analysis technique method, but some problems, could be misinterpreted by the measured distribution.

Most convenient method for measurement is based on top of a stack of five to ten sized openings from top to bottom. Particles are collected on the surface and presented in terms of percentage undersize or oversize versus

particle size and shape—can bias a distribution. It attributes the cause of variations in particle size, which, in turn, is affected by the characteristics of the powder being analyzed [4]. In a previous study, workers studied the effect of load—weight obtained for the particle size distribution

of model granulations [5]. Particle breakage occurred at increasing shaker speeds and times. According to the authors the reason the loading of material influences the time to reach equilibrium, defined in this article as the time at which the material that passes through the sieve, was due to particle attrition [5]. The authors finally concluded that a nonbiased analysis of particle size distribution should include an analysis of equilibrium times for each sieve [5].

An example of the use of sieve analysis was offered by Stevens, who addressed the effect of granule size distribution on the weight variation of tablets by constructing "isovariational curves" [6]. The intent of this evaluation was to define a geometric mean diameter and distribution that would result in an acceptable tablet weight variation. The geometric standard deviation was inverted and named the "R-value." Granulations with various mean diameters and distributions were prepared by sieving, recombining, and running on a rotary tablet press. The coefficient of variation (CV) of the tablet weight was recorded for each run. R values and CV for each geometric mean diameter were obtained from CV-R plots and then placed on a contour plot containing geometric mean diameter (abscissa), R value



**Fig. 3** Sieve analysis of lactose granules formed by massing and force screening showing effect of binder fluid level: circles, 15.3% v/v; squares, 18.4% v/v; upward triangles, 23% v/v; downward triangles, 30.6% v/v. (From Ref. 23.)

(ordinate), and CV (isovariational contour lines) [6]. Although the author claimed this must be done on a case-by-case (and a press-by-press) basis, these curves could be used to select the optimal mean granule size and distribution to minimize tablet weight variation [6].

### 3. Powder X-Ray Diffraction

A detailed description of powder X-ray diffraction is provided by Brittain et al. and the references cited therein [1]. This technique is used mostly to determine the crystalline form of a solid. It is especially useful in identifying the polymorphism of a solid. Understanding the effect of granulation on the form of the bulk drug has gained increasing attention in the past few years [7]. X-ray techniques provide the formulator with a first line of analysis in the determination of polymorph changes as a result of processing. In a joint American Association of Pharmaceutical Science–Federal Drug Administration (AAPS-FDA) report, an experimental rationale “where both the applicant [industry] and the FDA are in a better position to assess the possible effects of any variations in the solid state properties of the drug substance”

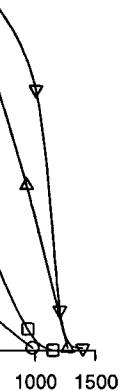
was provided [7]. Both X-ray diffraction (XRD) and nuclear magnetic resonance (NMR) were recommended for the identification of the drug substance in a drug product.

An example of the use of X-ray diffraction to identify form changes as a result of processing was provided by co-workers [8]. In this study, the effect of granulation on the polymorphism of (HMGCoA) reductase inhibitor was investigated. The bulk was in the anhydrous form during the wet granulation process. The granules were experimentally determined to be in the same form as the granulation to a relative humidity of 75%. The results caused a form conversion to the hemihydrate form. Experiments demonstrated the use of X-ray diffraction to identify powder X-ray diffraction, in the identification of the bulk form during granulation.

### 4. Thermal Analysis

Standard thermal methods of analysis include differential scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetry (TGA). A common application of thermal analysis in pharmaceuticals is based on thermal stability studies. LOD. In an LOD analysis, the sample is heated at a constant temperature near the boiling point of the solvent directly on an analytical balance. The weight loss is directly on an analytical balance. This technique is extensive in the study of drying parameters for various pharmaceuticals.

Differential-scanning calorimetry (DSC) is used to study the phase change of chloramphenicol (form I) [13]. The ingoing bulk form of chloramphenicol (form I) after it was wet-granulated was converted to a partially dehydrated form. Investigation of this form led to the identification of form I (form I). Extensive characterization of form I (hemihydrate form I-H) to form I (anhydrous form I) followed by a conversion from form I (anhydrous form I) to form I (anhydrous form I), finally, to melting at 185°C. The stable form was form I (by X-ray diffraction). The files of both anhydrous forms were not: the more stable form was form I (anhydrous form I) originally observed for form I.



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with a first line of analysis in  
a result of processing. In a joint  
cience-Federal Drug Adminis-  
rationale "where both the ap-  
position to assess the possible  
properties of the drug substance"

was provided [7]. Both X-ray and solid state nuclear magnetic resonance (NMR) were recommended techniques for assessing the crystalline form of the drug substance in a drug product [7].

An example of the use of X-ray techniques in the characterization of form changes as a result of wet granulation was reported by Morris and co-workers [8]. In this study a hydroxymethylglutarate coenzyme A (HMGCoA) reductase inhibitor was wet granulated with water. The ingoing bulk was in the anhydrous form, which then converted to an amorphous form during the wet granulation process [8]. The loss in crystallinity was experimentally determined using powder X-ray diffraction. Exposure of this granulation to a relative humidity (RH) environment, higher than 33% RH, caused a form conversion to a crystalline hydrate [8]. This series of experiments demonstrated the usefulness of a sophisticated technique, such as powder X-ray diffraction, in the assessment of the physical stability of the bulk form during granulation.

#### 4. Thermal Analysis

Standard thermal methods of analysis include differential-scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetry (TG). A common application of thermal analysis in the characterization of granulations is based on thermogravimetry and is known as loss on drying or LOD. In an LOD analysis, a sample of the granulation is heated at a temperature near the boiling point of water or solvent. The weight loss, recorded directly on an analytical balance, is due to the evaporation of water or solvent and is considered the residual moisture content of a granulation [9]. This technique is extensively used in the establishment of both granulation and drying parameters for wet granulation unit operations [10–12].

Differential-scanning calorimetry (DSC) was used in an evaluation of the phase change of chlorpromazine hydrochloride after wet granulation [13]. The ingoing bulk form (form II) converted to a hemihydrate (form I-H) after it was wet-granulated with a water-ethanol binder fluid. Form I-H converted to a partially dehydrated form (form I-H') after drying. An investigation of this form led the authors to another anhydrous polymorph (form I). Extensive characterization by DSC showed the transition from the hemihydrate (form I-H) to the anhydrous form (form I) at 40°–50°C, followed by a conversion from form I to form II at approximately 135°C, and finally, to melting at 185°–189°C [13]. By solution calorimetry, the most stable form was form I (by heat of solution). Although the dissolution profiles of both anhydrous forms were equivalent, the tableting characteristics were not: the more stable form did not exhibit the severe capping problems originally observed for form II [13].

## 5. Electrostatic Charge

Static charge is generated when two bodies come into intimate contact and then are separated. The surface of one of the contacting bodies attracts electrons from the other surface, thereby resulting in a negative charge. The forces of attraction and repulsion can cause significant problems in powder handling [14]. Gold and Palermo described a technique that measures the static charge of a powder as it passes out of a hopper [14]. The surface separation between particles occurs frequently in this dynamic environment. In the system proposed by these authors, powder was allowed to flow out of a hopper onto a glass receptacle. Directly beneath this receptacle was a copper disk that was attached to another copper disk beneath an ionostat. The ionostat recorded the voltage transmitted by the first disk. The material that was studied—acetaminophen—when granulated with either starch paste or syrup, exhibited a much lower static charge than the ungranulated powder [14]. The reduction in static charge was also correlated with improved flow out of the hopper [14].

## B. Bulk Level Characterization of Granulations

### 1. Surface Area

The surface area of particles and granules is an important property of a formulation to understand. Granulation properties are dependent on the size and surface area of ingoing materials [15,16]. The surface area of a granule or particle can also affect the dissolution rate of a solid. Gas adsorption techniques are the most common surface area method, although liquid penetration techniques have also been proposed [17]. One of the most common methods, developed by Brunauer, Emmet, and Teller, is called the BET method [18]. In this method an inert gas is adsorbed onto the surface of a solid at a low temperature and then desorbed at room temperature [1]. Either nitrogen or krypton are used as the adsorbate, and helium is usually used as the carrier gas for the adsorbate. Various concentrations of adsorbate in the carrier gas are used in this analysis to determine the volume of gas that is adsorbed in a monolayer on the solid. Eq. (1) is used to determine this value [18]:

$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m C} + \frac{(C - 1)P}{V_m C P_0} \quad (1)$$

where

$V$  = volume of gas adsorbed at pressure  $P$   
 $P$  = partial pressure of adsorbate

$C$  = a constant relating the adsorbate

$P_0$  = saturation pressure

$V_m$  = volume of gas a

A plot of  $P/V(P_0 - P)$  calculated from both the slope and surface area, in units of square

$$SSA = \frac{(V_m N_0 A_{cs})}{M}$$

where

$N_0$  = Avogadro's number

$A_{cs}$  = cross-sectional area

$M$  = mass of solid sample

Another method that has been used for powders is known as air permeability. A sample is subjected to a stream of air and the time for a drop is measured across the sample. The correction along the walls of pores is employed [19]. This correction is used on granulations or powders applied to compressed tablets. More detail later (see Sec. II).

### 2. Granule Porosity

Mercury intrusion methods are used to determine the size and distribution to both the method, excess pressure is applied for the smallest pores to be measured. Pore size, pressure and pore radius, known as the Washburn equation, is used to calculate pore size distribution.

$$\Delta P = - \left( \frac{2\gamma}{r} \right) \cos \theta$$

where

$\Delta P$  = pressure difference  
 $\gamma$  = surface tension

come into intimate contact and contacting bodies attracts electricity in a negative charge. The significant problems in powder is a technique that measures the of a hopper [14]. The surface in this dynamic environment. powder was allowed to flow out beneath this receptacle was a hopper disk beneath an ionostat. d by the first disk. The material granulated with either starch ic charge than the ungranulated e was also correlated with im-

## Granulations

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(1)

ure  $P$ 

$C$  = a constant relating the heats of adsorption and condensation of the adsorbate

$P_0$  = saturation pressure of adsorbate at experimental temperature

$V_m$  = volume of gas adsorbed in monolayer of solid

A plot of  $P/V(P_0 - P)$  versus  $P/P_0$  yields a straight line.  $V_m$  is calculated from both the slope and intercept of this line [18]. The specific surface area, in units of square meters per gram is calculated using Eq. (2):

$$SSA = \frac{(V_m N_0 A_{cs})}{M} \quad (2)$$

where

$N_0$  = Avogadro's number

$A_{cs}$  = cross-sectional area of adsorbate

$M$  = mass of solid sample

Another method that has been proposed for measuring the surface area of powders is known as air permeability [19]. A column packed with powder is subjected to a stream of air. The system is sealed off and the pressure drop is measured across the bed. To take into account the "slip" of gas along the walls of pores a modification of the governing equation is employed [19]. This correction minimizes the apparent dependence of specific surface area on air pressure. Although this method has not been extensively used on granulations or powders in the pharmaceutical sciences, it has been applied to compressed tablets [20]. This application will be described in more detail later (see Sec. II.C.2.d).

## 2. Granule Porosity

Mercury intrusion methods are routinely applied in the determination of pore size and distribution to both granulations and tablet compacts [21]. In this method, excess pressure is applied to a nonwetting liquid, such as mercury, for the smallest pores to be filled [21]. A relation between the applied pressure and pore radius, known as the Washburn equation [Eq. (3)], is then used to calculate pore size opening [21]:

$$\Delta P = - \left( \frac{2\gamma}{r} \right) \cos \theta \quad (3)$$

where

$\Delta P$  = pressure difference across interface

$\gamma$  = surface tension of the penetrating liquid

$\theta$  = contact angle of the penetrating liquid  
 $r$  = pore radius

In this analysis the sample is introduced into the chamber, degased, and then completely covered with mercury. Pressure is incrementally applied, and the volume of mercury that penetrates into the pores is recorded [1]. A plot of cumulative volume intruded versus pressure is obtained and converted to cumulative volume versus pore radius. The pore size distribution is obtained by differentiating the latter curve [1].

In an early paper, Strickland et al. used mercury intrusion to differentiate granulations based on granule porosity [22]. The authors were able to compare a starch paste granulation prepared by wet-massing starch with sodium bicarbonate and a dry-granulated (slugged) aspirin formulation using this technique. The intragranular porosity of the dry granulated material was 2.9%, whereas the starch paste wet granulation was 29% [22]. This difference can impinge on the tableting behavior of a granulation and will be discussed in further detail later (see Sec. II.C.2.d).

Ganderton and Hunter used mercury intrusion to compare the intragranular porosity of granulations manufactured by different processes [23]. Calcium phosphate was granulated with a 10% dextrose-water binder and the comparison was made between a pan granulator and a Z-blade mixer. A plot of intragranular porosity versus binder level (denoted as moisture content) is shown in Fig. 4. A significant decrease in intragranular porosity was observed when massed in a Z-blade mixer and then screened [23]. An opposite trend was noted for lactose granulated with water as a binder. The results of this study suggest that the physicochemical properties of the powder being granulated can have a significant influence on the sensitivity of granule properties to granulation process.

### 3. Granule Strength

The strength of granules is a property that is routinely measured in the development of a formulation. In a classic treatment of the topic, Rumpf has described numerous mechanisms that contribute to granule and agglomerate strength: (a) solid bridges between particles, (b) interfacial forces and capillary pressure in moveable liquid surfaces, (c) adhesional and cohesive forces in bonding, (d) attraction between solid particles, and (e) particle shape-influenced mechanical interlocking [24]. Rumpf considered the tensile strength of the particle bond to be the most important factor in the determination of agglomerate strength [24]. He proposed a direct test of the tensile strength of agglomerates; although the size of the granules that were tested were approximately 2.5 cm (1 in.) in diameter.

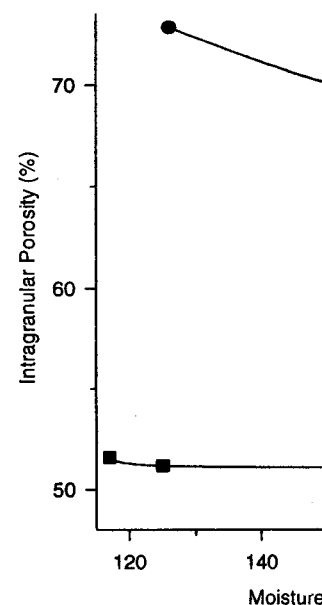


Fig. 4 The effect of moisture on intragranular porosity of calcium phosphate granules processed by a Z-blade mixer and screened. (From Ref. 23.)

Several methods have been used for the measurement of the tensile strength of granules. The method of Pilpel and subsequently Gold et al. [23,25,26]. The method involves moving a platen across the granule profile and the forces measured are interpreted as being due to the tensile strength of mass or force [26]. A disadvantage of this method is that, owing to the lack of understanding of the load acts.

Mehta and co-workers [27] have noted the inherent variability of the tensile strength in measuring the strength of granules. Many samples must be measured and the crushing measurement method is used to estimate granule strength by monitoring the dry sieve analysis.

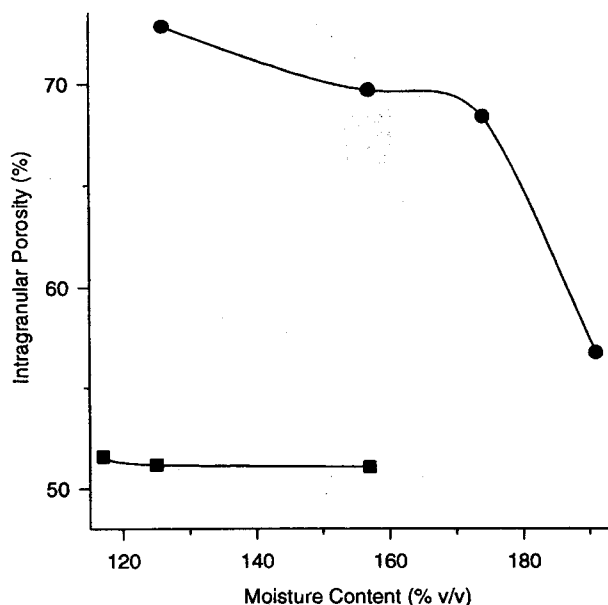
liquid

the chamber, degased, and then s incrementally applied, and the pores is recorded [1]. A plot of e is obtained and converted to pore size distribution is obtained

ed mercury intrusion to differ- ity [22]. The authors were able red by wet-massing starch with (gged) aspirin formulation using the dry granulated material was ion was 29% [22]. This differ- r of a granulation and will be C.2.d).

intrusion to compare the intra- red by different processes [23]. 0% dextrose-water binder and anulator and a Z-blade mixer. A level (denoted as moisture conse in intragranular porosity was r and then screened [23]. An ted with water as a binder. The chemical properties of the pow- influence on the sensitivity of

it is routinely measured in the treatment of the topic, Rumpf ntribute to granule and agglom- rticles, (b) interfacial forces and s, (c) adhesional and cohesional solid particles, and (e) particle [4]. Rumpf considered the tensile t important factor in the deter- e proposed a direct test of the e size of the granules that were diameter.



**Fig. 4** The effect of moisture content on the porosity of -12+16-mesh calcium phosphate granules processed for 10 min: circles, pan granulated; squares, massed and screened. (From Ref. 23.)

Several methods have been proposed in the pharmaceutical literature for the measurement of the strength of granules. One way of measuring granule strength by directly crushing them uses a test proposed by Harwood and Pilpel and subsequently modified by both Ganderton and Hunter and by Gold et al. [23,25,26]. The force required to crush the granule is recorded when a platen is moved at a constant strain rate. Deflections in the load profile are interpreted as break points and the strength is recorded in units of mass or force [26]. A direct measurement of tensile strength is difficult owing to the lack of understanding of the surface area on which the applied load acts.

Mehta and co-workers have criticized this method because of the inherent variability of the properties of granules as well as for the difficulty in measuring the strength of granules smaller than 40 mesh [27]. Many samples must be measured and results averaged to make the granule-crushing measurement meaningful. In their method, ball milling is used to estimate granule strength by following granule attrition [27]. Attrition was monitored using dry sieve analysis. Their method correlated very well with



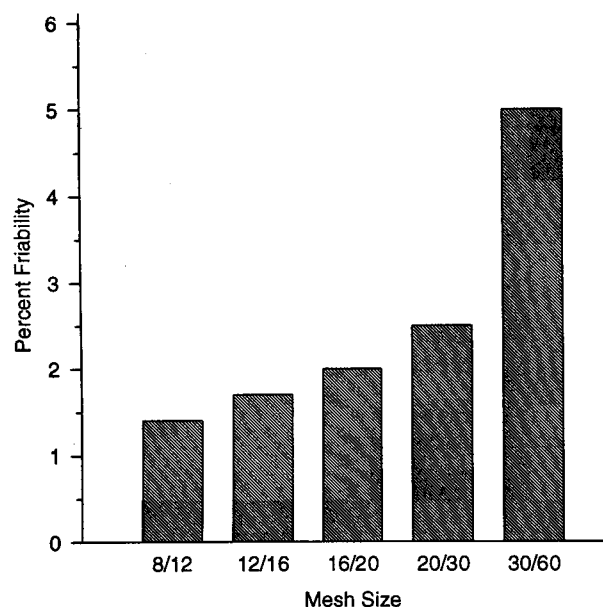


Fig. 5 Friability of sulfadiazene granulations. (From Ref. 29.)

the Harwood-Pipel method, with a much better coefficient of variation for their technique (1–5% for the ball-milling method and 50–80% for the direct-crushing strength method) [27].

Another attrition method used in determining granule strength is determination of the friability of granulations [28,29]. In this measurement a friabilator is charged with the granulation to be tested and then rotated a set number of times. The percentage loss of mass for a particular size is usually the value that is represented in a granule friability analysis [29,30]. This method is useful to identify property differences as a function of granule size within a granulation [29]. An example is given for a sulfadiazine granulation in Fig. 5.

#### 4. Powder Flowability and Density

A formulation scientist will most likely turn to granulation more often than not to improve the flowability or reduce the specific volume of a blend. Some measurement, therefore, is required to monitor the improvement in flowability. Specific volume is a property of a powder that is believed to affect powder flowability. Specific volume is determined by pouring a known mass of blend into a graduated cylinder. The volume is read off the cylinder

and the specific volume is of the blend [31]. The compressed volume is read off this time. The graduated cylinder is then inverted. This vibration reduces the volume of the granules in the cylinder. The percentage compression is calculated as follows:

$$\% \text{ Compressibility} = \frac{V - V_c}{V} \times 100$$

where

$P$  = packed density (g/cc)

$A$  = bulk density (g/cc)

The percentage compressibility is a measure of the granule strength [33]. This index is interpreted such that the lower the compressibility, the poorer the granule strength. In the evaluation of a granulation, the authors evaluated the sucrose-lactose-starch granulation on a 30-kg scale [34]. The compressibility was measured as well as the kneading time as well as the

Powder flowability can be measured by the "orifice" technique [9,33]. This technique is used because a hopper is charged with the granulation and the charge is measured [35]. A relation between the flow rate and the size of the orifice. Pipel describes this technique in detail [35]. The flow rate is measured by a visual analysis, and energy

A more fundamental method of measuring powder flowability is by assessing interparticulate forces. The angle of repose is dependent on interparticulate forces. The angle of repose is obtained by pouring the powder into a cone and then slowly raising the angle of the heap that is formed. In general, the higher the angle of repose, the poorer the flow. A dynamic, or kinetic, angle of repose is obtained by rotating a drum with blend and rotating the drum at a constant speed, recording how high the blend rises. The angle of repose will be 1° for some problems with this technique. The angle of repose of blends determined by this method, a result that is in agree-

and the specific volume is calculated by dividing the volume by the mass of the blend [31]. The compressibility of a blend can also be determined at this time. The graduated cylinder is vibrated on a shaker for a time period. This vibration reduces the volume that the blend occupies in the graduated cylinder. The percentage compressibility is calculated as [32]:

$$\% \text{ Compressibility} = \frac{100 \times (P - A)}{P} \quad (4)$$

where

$P$  = packed density (after vibration)

$A$  = bulk density (untapped)

The percentage compressibility is commonly known as Carr's index [33]. This index is interpreted in the following way: the higher the compressibility, the poorer the flowability. An example of how this was used in the evaluation of a granulation process was reported by Ertel et al. [34]. In this report, the authors evaluated effects of the scale of preparation of a sucrose-lactose-starch granulation using Lodige granulators at the 4- and 30-kg scale [34]. The compressibility of the granulations was dependent on the kneading time as well as the scale of preparation.

Powder flowability can be directly measured using the "flow through an orifice" technique [9,35]. This test is close to an actual "use test," because a hopper is charged with the blend and the flow rate during discharge is measured [35]. A variation on this test is achieved by determining the relation between the flow rate of a blend and the diameter of the opening of the orifice. Pilpel describes the various methods of data analysis for this technique in detail [35]. These methods include empirical equations, dimensional analysis, and energy considerations [35].

A more fundamental evaluation of powder flowability can be obtained by assessing interparticulate friction. The angle of repose is a parameter that is dependent on interparticulate friction and cohesion [35-38]. The static angle of repose is obtained by filling an open-ended cylinder with the blend and then slowly raising the cylinder, allowing the powder to flow out. The angle of the heap that is formed is called the static angle of repose [35]. In general, the higher the angle of repose the poorer the flowability of the blend. A dynamic, or kinetic, angle of repose can be obtained by charging a hollow drum with blend and rotating it. The angle of repose can be calculated by recording how high the blend travels up the wall of the drum [32,35]. This angle of repose will be 1°-5° lower than the static angle [35]. There are some problems with this technique, however. Danish has found that the angle of repose of blends did not correlate with the flow through an orifice data, a result that is in agreement with other authors [36,39].

A better method for determining the cohesive and frictional effects of particles is by using a shear cell [37,40,41]. There are various cell configurations, the most popular proposed by Jenike (Fig. 6) [40]. In the Jenike cell, a powder is loaded and then compressed by twisting the lid of the cell. The number of twists required to load the powder to the point at which the resistance to shear (measured as stress applied to ring around the bed) is constant. This phase of the test is known as "shear consolidation." The load is reduced and the resistance to shear is then recorded. A "yield locus" of this shear stress versus the reduced load is obtained and used to calculate various flow-related parameters [35,37,40]. Numerous parameters can be derived from the yield locus: flow factor, shear index, cohesion, tensile strength, effective angle of internal friction, and unconfined yield stress [37]. All of these parameters can be used in the characterization of powder flowability.

Other shear cells have been used to characterize the flowability of blends. Carr and Walker describe an annular shear cell that measures the resistance to the angular movement of the shoe that is placed on top of the powder [42]. The advantage to this type of design is that unlimited travel of the shoe provides an opportunity to measure successive initial consolidation loads without reloading the powder [42]. Hiestand and later on, Amidon and Houghton, describe a plate-type shear cell that is similar to the Jenike shear cell, with the exception that the powder bed is unconstrained at the edge of the bed [41,43].

Sinko and co-workers have demonstrated the usefulness of the plate-type shear cell in directly measuring the improvement in flowability that is

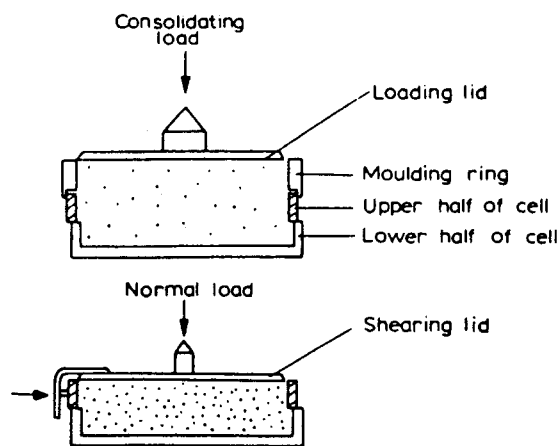


Fig. 6 Schematic of Jenike shear cell. (From Ref. 37.)

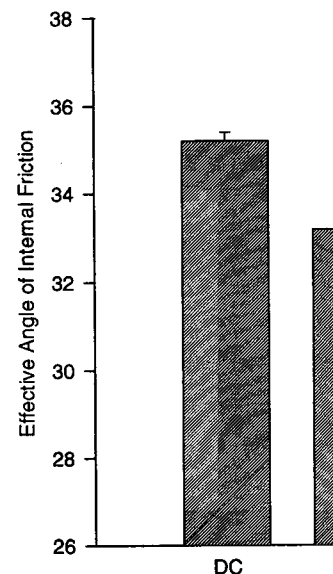


Fig. 7 The effect of process on the effective angle of internal friction; DC, direct compression; RC, roller compaction.

afforded by wet granulation. The flowability, estimated by the effective angle of internal friction, estimates the powder's resistance to shear. The normal load, was used to track the resistance to shear through dry and wet granulation. The effective angle of internal friction for a direct compression formulation of near equivalent granulation resulted in a greater resistance to shear than a similarly sized

## 5. In-Process Characterization

One of the more useful in-process measurements is the measurement of the rheological properties. Sinko and co-workers were able to identify the endpoint of the granulation process. The cumulative energy of the torque-time curve, was proportional to the granulation. It can be used to identify granulation endpoints.

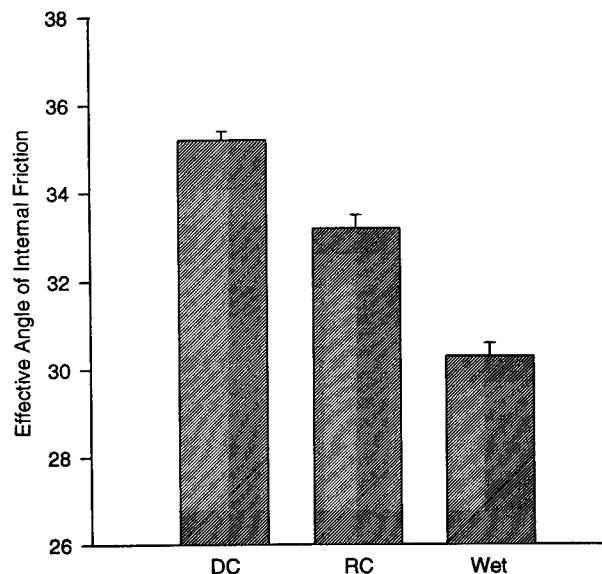
hesive and frictional effects of . There are various cell configurations (Fig. 6) [40]. In the Jenike cell, the lid of the cell is twisted by twisting the lid of the cell. The powder is moved to the point at which the lid is twisted (ring around the bed) is 'shear consolidation.' The load is recorded. A "yield locus" of the powder is obtained and used to calculate various parameters. Numerous parameters can be determined: shear index, cohesion, tensile strength, and unconfined yield stress [37]. The characterization of powder flow-

characterize the flowability of a powder, a shear cell that measures the effective angle of internal friction is placed on top of the powder. The design is that unlimited travel of the powder is possible. To measure successive initial consolidation, the powder is consolidated in a shear cell that is similar to the Jenike cell. The powder bed is unconstrained

ated the usefulness of the plate-shear cell in improving flowability that is

cell  
cell

Ref. 37.)



**Fig. 7** The effect of process on the flowability of lactose-based granulations: DC, direct compression; RC, roller compacted; Wet, wet granulated. (From Ref. 44.)

afforded by wet granulation [44]. In this study, the measurement of flowability, estimated by the effective angle of internal friction, a parameter that estimates the powder's resistance to shear stress as a function of applied load, was used to track the potential improvement in flowability achieved through dry and wet granulation. A comparison of the effective angle of internal friction for a direct compression, wet-granulated, and dry-granulated formulation of near equivalent composition is provided in Fig. 7. Wet granulation resulted in a greater improvement in the flowability of the formulation than a similarly sized dry granulation.

### 5. In-Process Characterization

One of the more useful in-process physical characterization techniques is the measurement of the rheology of wet-massed material. Hancock and co-workers were able to identify the liquid saturation point, denoted as the endpoint of the granulation process, using a mixer torque rheometer [45]. The *cumulative energy of mixing* (CEM), defined as the area under the torque-time curve, was proposed as a parameter that could be used to identify granulation endpoints. This parameter was also proposed as one that

could be measured at any scale because this value was independent of mixing intensity, a parameter that will vary with scale [45].

For a placebo granulation, Rowe and Parker used this type of device to characterize the granulation prepared with various liquid-binder levels at the 25- and 100-L scale [46]. The authors proposed that a "power" number and "pseudo-Reynolds" number relation existed, such that endpoints that were obtained at different scales of manufacture could then be related to each other. In this way the mixer torque rheometer could then be used to assess the quality of the granulation and, eventually, used to identify the true endpoint of the granulation when the product was transferred up in scale [46].

Attempts have been made at measuring the torque experienced at an impeller in a high shear granulator. The intention of this measurement is to define the wet mass endpoint during granulation. An example of this measurement was reported by Ritala and Virtanen [47]. These authors evaluated the effect of the ingoing particle size of lactose on this type of measurement and found that larger-sized lactose required more force and energy to granulate. They were able to correlate the difference in these parameters with final granule size. Interestingly, the impeller load during the granulation of lactose reaches a plateau value and does not increase [47]. The authors hypothesize that once this point is reached, the densification of the lactose granule ceases [47]. A very detailed description of wet mass endpoints and methods to measure them has been provided in a review by Kristensen and Schaefer [48].

Holve and Harvill have described an in-line particle size measurement system that is based on laser diffraction [49]. Although this method is better-suited to measurements in free-flowing streams, the technique produces data that is equivalent to data produced by manual, off-line methods. The product is sampled from the stream and passed through a laser beam. The data is collected and numerically modified for particle size analysis [49]. Although this technique may not be directly applicable to high shear or low shear wet-massing methods, it could possibly be used for fluid bed or dry granulation unit operations.

### C. Bulk Level Characterization of Tablets

The characterization of granulations does not stop at the granulation. An understanding of the effect of granulation, the unit operation, on tablet core manufacturing and, ultimately, dosage form performance is an important goal of a formulation scientist. Much of the literature that is devoted to the characterization of tablets can be separated into two points of view: char-

acterization of the compact and the granulation. Both are explored

#### 1. Compaction Process

##### a. Dynamic Compaction

of tablet presses have allowed the opportunity to gain more precise data on punch force and punch displacement. This allows for a more detailed analysis of the energy expended in the compaction process. The punch force-displacement curve is caused by die wall friction and the force transmitted to the punch. The energy analysis [51,52]. The energy term, owing to the large amount of energy generated during compaction.

de Blaey and co-workers

granulation by compressing a sample. They considered the sum of the elastic and plastic deformation. The second component is the work of compression. Subtracting the work from the total work from the first results in an estimate of the deformation of the granule. Mitchell refined the determination of the work of compression by calibrating the deflection of the punch against the theoretical calculation of the work of compression. He was able to demonstrate a method for determining the work of compression having to measure the displacement of the punch. Pope have suggested that energy can be used to characterize the energy used during compaction. That the relation between the work of compaction may be more

Heckel analysis is a common method, mostly because of the wide range of data. In this analysis, the volume change is measured. The volume is converted to a pressure using the following

$$\ln \left[ \frac{1}{1 - \rho_{app}} \right] = kP + \text{constant}$$

s value was independent of mix-  
h scale [45].

Parker used this type of device  
h various liquid-binder levels at  
proposed that a "power" number  
existed, such that endpoints that  
facture could then be related to  
heometer could then be used to  
eventually, used to identify the  
product was transferred up in scale

ng the torque experienced at an  
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lation. An example of this mea-  
en [47]. These authors evaluated  
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erence in these parameters with  
r load during the granulation of  
not increase [47]. The authors  
the densification of the lactose  
tion of wet mass endpoints and  
d in a review by Kristensen and

n-line particle size measurement  
. Although this method is better-  
ams, the technique produces data  
al, off-line methods. The product  
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icle size analysis [49]. Although  
ble to high shear or low shear  
used for fluid bed or dry gran-

## Tablets

not stop at the granulation. An  
he unit operation, on tablet core  
n performance is an important  
literature that is devoted to the  
into two points of view: char-

acterization of the compaction process and characterization of the finished  
product. Both are explored in the following.

### 1. Compaction Process

*a. Dynamic Compaction Analysis.* Advances in the instrumentation  
of tablet presses have allowed many industrial and academic scientists the  
opportunity to gain more process-related data. Instrumentation of both punch  
force and punch displacement during compaction allows the scientist to con-  
duct an analysis of the energy or work of compaction [50]. The value of the  
work expended in the compression of a powder is obtained by integrating  
the punch force-displacement curve results [50]. To remove energy losses  
caused by die wall friction during compression, the area of the curve under  
the force transmitted to the lower punch-displacement of the upper punch  
curve (for one-sided punch movement) was proposed as a better method of  
energy analysis [51,52]. This value of energy is called an *apparent net en-  
ergy* term, owing to the lack of understanding of the contribution of radial  
energy generated during compression [53,54].

de Blaey and co-workers have proposed a modification of this calcu-  
lation by compressing a sample twice [53,55]. The first compression is con-  
sidered the sum of the elastic and plastic components of work during com-  
pression. The second compression is assumed to be pure elastic work.  
Subtracting the work from the second compression from the work obtained  
from the first results in an estimate of the work associated with the plastic  
deformation of the granulation during compression [53,55]. Oates and  
Mitchell refined the determination of energy of compaction in a rotary press  
by calibrating the deflection of a press and incorporating this deflection into  
the theoretical calculation of punch displacement [56]. In this way, they were  
able to demonstrate a method for calculating the work of compaction without  
having to measure the displacement-time profile of the punch. Krycer and  
Pope have suggested that energy of compaction alone is not enough to char-  
acterize the energy used during the compaction process [50]. They suggested  
that the relation between the work of failure of a tablet and the net energy  
of compaction may be more useful [50,57].

Heckel analysis is another popular method of compaction analysis,  
mostly because of the widespread availability of press instrumentation. In  
this analysis, the volume change is monitored during the compression event.  
The volume is converted to an apparent density and related to compression  
pressure using the following empirical relation [Eq. (5)]:

$$\ln \left[ \frac{1}{1 - \rho_{app}} \right] = kP + A \quad (5)$$

where

$\rho_{app}$  = the apparent density of the compact

$P$  = compression pressure

$k$  = the inverse of the mean yield pressure of the material

High values of the slope suggest the material being compressed has high ductility or plasticity, whereas low values indicate the material has low ductility. York, however, has suggested that the experimental conditions can influence the values obtained using this analysis [58]. Compaction rate, sample size, particle size, degree of lubrication, as well as other conditions, influence the values obtained for crystalline lactose [58–60].

A sophisticated method for characterizing the time-dependent, or viscoelastic, properties was described by Danielson et al. and, later, Morehead and Rippie [61,62]. The punch pressure–die wall pressure–time profiles obtained during the compaction in a rotary press are used to extract material parameters that describe the time-dependent nature of the material's response. A direct indication of the viscoelastic response of a material during compression is observed as an offset lag in time between the maximum in punch pressure and the maximum in die wall pressure [62]. Offset times between punch–displacement maxima and punch–force maxima were used by Dwivedi and co-workers in the determination of stress relaxation behavior of materials undergoing compression in a rotary tablet press [63]. The authors implied that deformation mechanisms could be differentiated by evaluating the dependence of the offset time on compression pressure. The materials that exhibited the greatest time dependence were characterized as “plastic-deforming” [63].

*b. Compaction Simulation.* The characterization of the compaction properties of a granulation can be obtained using a compaction simulator. A compaction simulator is a computer-controlled tablet press that, if properly instructed, can simulate the real-time dynamics of a production tablet press. The advantage to this research tool is that specific punch displacement profiles can be used to obtain clean mechanical response. An example of the controlled nature of the analysis is provided by Roberts and Rowe [60]. “Sawtooth” profiles, or constant-velocity punch displacement, were used in a logarithmic range of rates to characterize the mechanical response of materials that ranged from plastically deforming to fragmenting [60]. These same authors also proposed a strain rate sensitivity index to characterize the time-dependent properties of materials during compression [59].

Percolation theory has also been used to analyze data obtained on a compaction simulator [64]. The application of percolation theory to the compaction process is based on the observation that a compact containing par-

ticulate matter crosses over. Thresholds mark this transition in consolidation mechanisms and can also be used to characterize

## 2. Tablet Characterization

*a. Tablet Strength.* The most commonly used method to characterize tablet strength is by the number of references to the method of characterization of the resistance to fracture, exactly what it sounds like. The force of which is driven against the tablet is recorded as the force required to fracture for determining the strength [68–70]. These methods rely on the fundamental mechanical properties of the particulates [24,71]. Diameter, shape, texture, whereas compact or tablet strength, fracture that is orthogonal to the

*b. Mechanical Properties.* The mechanical properties of the particulate material, characteristics and resultant properties of granules and compaction, the actual compaction process, mechanical energy, can be estimated [73]. Bassam and co-workers have shown for which the load and deformation of elastic, or Young's, modulus

Elasticity is an important property. The response of granules can cause a significant important mechanical properties. It has been described as one of the true area of contact between particles [71]. The plasticity of granules using indentation methods to measure the tablet or compact compression is recorded. The depth of the indentation with this force, in the calculation is directly related to yield strength (yielding) [72,75]. A material is considered to have higher p

compact

pressure of the material

the material being compressed has values indicate the material has low at the experimental conditions can analysis [58]. Compaction rate, sam- on, as well as other conditions, e lactose [58–60].

izing the time-dependent, or vis- elson et al. and, later, Morehead e wall pressure–time profiles ob- press are used to extract material ent nature of the material's re- tic response of a material during n time between the maximum in wall pressure [62]. Offset times punch–force maxima were used nation of stress relaxation behav- n a rotary tablet press [63]. The isms could be differentiated by ne on compression pressure. The ependence were characterized as

characterization of the compaction using a compaction simulator. A lled tablet press that, if properly nics of a production tablet press. specific punch displacement pro- cal response. An example of the ded by Roberts and Rowe [60]. ouch displacement, were used in the mechanical response of ma- ing to fragmenting [60]. These nsitivity index to characterize the ing compression [59].

ed to analyze data obtained on a of percolation theory to the com- n that a compact containing par-

ticulate matter crosses over from a loose powder to a coherent compact. Thresholds mark this transition and can be used to characterize different consolidation mechanisms [64–67]. The slope of the compression curves can also be used to characterize the material [64,66].

## 2. Tablet Characterization

*a. Tablet Strength.* The crushing strength of tablets is the most widely used method to characterize the end product. This observation is supported by the number of references to various granulation unit operations and the characterization of the resultant product. The crushing of tablets implies exactly what it sounds like; a tablet is placed in between two platens, one of which is driven against the side of the tablet. The strength of the tablet is recorded as the force required to crush the tablet [9]. More exact methods for determining the strength of tablets as compacts have been proposed [68–70]. These methods rely on the determination of tensile strength, a fundamental mechanical property that governs the strength of bonds between particulates [24,71]. Diametric compression methods are compressive in nature, whereas compact or tablet loading down the center line results in tensile fracture that is orthogonal to the transit of the platen [68,70].

*b. Mechanical Properties.* It has long been known that the mechanical properties of the particles being compressed dominate the compression characteristics and resultant strength of the compact [71,72]. The mechanical properties of granules and compacts can be determined independently from the actual compaction process. Elasticity, the instantaneous recovery of mechanical energy, can be estimated using three- or four-point beam bending [73]. Bassam and co-workers described the bending of 10-cm  $\times$  1-cm beams for which the load and deflection are recorded and used in the calculation of elastic, or Young's, modulus [73].

Elasticity is an important mechanical property because the elastic response of granules can cause problems in the hardness of tablets. Another important mechanical property is known as plasticity or ductility. Plasticity has been described as one of the properties that influences the decrease in the true area of contact between particles or granules during compression [71]. The plasticity of granules or particles can be indirectly determined using indentation methods [74]. A steel sphere is driven into the surface of the tablet or compact comprised of powder or granules and the force is recorded. The depth of the indentation or the recovered dent is used along with this force, in the calculation of indentation hardness, a parameter that is directly related to yield pressure (also known as the critical stress for yielding) [72,75]. A material that has a low value of indentation hardness is considered to have higher plasticity.



The fracture propensity of a material can also be determined using beam-bending techniques [76]. A notch of known length is carved into a beam and the load required to break the beam is used in the calculation of what is known as the critical stress intensity factor  $K_{IC}$  [76]. The higher the value, the less brittle the material is. Beam bending has also been used to assess the viscoelasticity of materials. Radebaugh et al. applied a torsional strain (twisting) on a beam at a specific frequency [77]. The loss and storage modulus of a material could be directly measured with this technique.

*c. Tableting Indices.* No one mechanical property governs the successful compaction of a material. Recognizing this, Hiestand and Smith developed dimensionless numbers that take into account different mechanical properties [78]. These dimensionless numbers were introduced in the literature as tableting indices [78]. The first index, known as the strain index, is an estimate of the elastic response normally associated with decompression. The second index, known as the bonding index, is an estimate of the survival of bonding contact area during decompression. This is calculated by dividing the tensile strength of a compact by its indentation hardness [78]. The final index, known as the brittle fracture index (BFI), is defined by Eq. (6) [78]:

$$BFI = \frac{1}{2} \left( \frac{\sigma_T}{\sigma_{T0}} - 1 \right) \quad (6)$$

This index describes the material's ability to relax a concentration of stress built up at a macroscopic defect. Experimentally, the defect (a hole) is placed at the center of a compact and the tensile strength is determined [78]. A high value for BFI indicates the formulation is brittle. The BFI was used by Itiola and Pipel to guide them on the selection of the type and level of binder [79]. The granules were produced by wet granulation.

*d. Tablet Porosity.* The porosimetry methods described in the foregoing for granules can be applied to the intact tablet to provide an understanding of the pore structure of the compact. The structure of the compact has been cited as an important factor in controlling disintegration, dissolution, adsorption, diffusion, and strength [80,81]. The principles that govern mercury intrusion porosimetry for granules can be directly applied to tablets [82]. Selkirk and Ganderton explored the effect of granulation on the pore structure and strength of both sucrose and lactose tablets [82]. They found that weak granules, generated by wet massing with lower volumes of binder fluid, produced stronger tablets than when strong granules were used. Their hypothesis was that the weak granules fragmented during compaction thereby producing a larger bonding surface area. This hypothesis was supported by the reduction in the mean pore size of tablets made with the

weaker granules. Here, the size of ungranulated material

An interesting application reported by Gucluyildiz and others [80] was the effect of pores within a tablet and the relationship between the pore size and the active drug was assessed for an aspirin-starch formulation. The stability at a level of 3%. Pore size was most effective at reducing the level [80]. The authors hypothesized that the diffusion of water through the pores reduced the transport of water, resulting in a reduction in the degradation rate.

The air permeability of a compact after fragmentation after compaction are converted into specific surface area using the Kozeny-Carmen equation [2]. The surface area can be ascertained with this technique. The surface area of saccharose and sodium chloride tablets showed a greater increase in the specific surface area with increasing compression pressure than is illustrated in Fig. 8. The specific surface area as an indicator of fragmentation during compression was used by the authors as a result of the relationship between the air permeability and the surface area during compression. These results were used in the method, and the differences between the two materials as saccharose, is studied [81,83-86].

### 3. Performance Testing

Ultimately, the formulation of a drug must be in the dosage form. This assessment of the dosage form such as disintegration or dissolution could be used to assess the performance test in human volunteers. The dissolution test is routinely used to compare different formulations. The formulation iterations will be generally relied on for routine

can also be determined using known length is carved into a am is used in the calculation of y factor  $K_{IC}$  [76]. The higher the bending has also been used to baugh et al. applied a torsional uency [77]. The loss and storage asured with this technique.

anical property governs the suc- ing this, Hiestand and Smith de- to account different mechanical ers were introduced in the liter- ex, known as the strain index, is associated with decompression. ex, is an estimate of the survival on. This is calculated by dividing entation hardness [78]. The final BFI), is defined by Eq. (6) [78]:

(6)

ility to relax a concentration of perimentally, the defect (a hole) e tensile strength is determined mulation is brittle. The BFI was e selection of the type and level l by wet granulation.

methods described in the fore- tact tablet to provide an under- ct. The structure of the compact ntrolling disintegration, dissolu- ,81]. The principles that govern can be directly applied to tablets ffect of granulation on the pore lactose tablets [82]. They found ng with lower volumes of binder strong granules were used. Their fragmented during compaction area. This hypothesis was sup- e size of tablets made with the

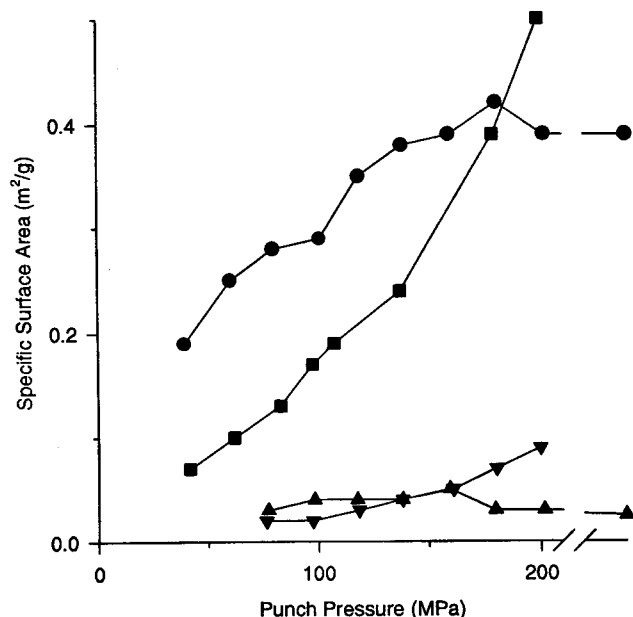
weaker granules. Here, the pore size of these tablets approached the pore size of ungranulated materials [82].

An interesting application of mercury porosimetry on intact tablets was reported by Gucluyildiz and co-workers, for which a probe of pore structure within a tablet and the relation between the pore size and the stability of the active drug was assessed [80]. The addition of silicon dioxide to an aspirin-starch formulation resulted in an improvement in the chemical stability at a level of 3%. Pore size measurements indicated that silicon dioxide was most effective at reducing the size and volume of coarse pores at this level [80]. The authors hypothesized that the reduction of these pores, coupled with the diffusion of salicylic acid, the degradation product, into these pores reduced the transport of water vapor into the tablet, thereby causing a reduction in the degradation rate.

The air permeability of tablets has also been used to quantify granule fragmentation after compaction [20]. Pressure differences across the tablet are converted into specific surface area within a tablet, by using the modified Kozeny-Carmen equation [20]. The fragmentation propensity of granules can be ascertained with this technique. In the comparison of the compression of saccharose and sodium chloride, Alderborn and co-workers observed a greater increase in the specific surface area of saccharose as a function of compression pressure than that found for sodium chloride [20]. This trend is illustrated in Fig. 8. The authors interpreted this greater increase in specific surface area as an indication of a greater propensity for granule fragmentation during compression. The differences in specific surface area between the air permeability method and the BET method were rationalized by the authors as a result of the formation of microcracks or voids formed during compression. These will be accessible only by the gas adsorption method, and the differences may be magnified when a brittle system, such as saccharose, is studied [20]. This interpretation has been supported by other observations of the compression characteristics of these materials [81,83-86].

### 3. Performance Testing

Ultimately, the formulation scientist will need to assess the performance of the dosage form. This assessment could be achieved through in vitro testing, such as disintegration or dissolution testing. Alternatively, in vivo testing could be used to assess the performance of the dosage form. A bioequivalence test in human volunteers is an example of an in vivo test that is routinely used to compare dosage form performance. It is doubtful that formulation iterations will be tested in vivo, because such in vitro tests are generally relied on for routine performance testing.



**Fig. 8** Weight-specific surface area as a function of compaction pressure: (a) measured by air permeametry for sodium chloride tablets (downward triangles) and saccharose tablets (squares); (b) measured by the BET method for sodium chloride tablets (upward triangles) and saccharose tablets (circles). (From Ref. 20.)

*a. Disintegration.* The disintegration of a dosage form into its primary granules or particles is the first step toward the dissolution of the drug substance. The rate of penetration of a liquid into the dosage form is generally governed by the surface tension of the penetrating solution and the contact angle of the solid [87]. Disintegration methods usually involve the submersion of the dosage form in the dissolution medium or in water. The time required for dosage form breakdown is recorded as the disintegration time.

The characterization of disintegrated dosage forms and of the disintegration process itself has been reported in the literature [87–89]. Rubenstein and Wells used a Coulter counter to measure the surface area of disintegrated phenylbutazone tablets [88]. They were able to correlate the surface area of the disintegrated tablets with the percentage of drug dissolved at 60 min. Forlano and Chavkin found the disintegration time of tablets increased to a maximum with decreasing granule size [89]. The decrease in disintegration times was related to the capping propensity of the tablets, thus suggesting that the mechanical integrity of the tablets played a role in the

disintegration time [89]. No correlation was found between the physicochemical properties of the granules and the disintegration of tablets [87]. They found that the contact angle of the penetrating solution, the surface tension, the mean diameter of capillaries, and the surface area of the granules altered with compression force. The authors determined that the disintegration time could be applied to the

*b. Dissolution.* An alternative method of characterizing a dosage form is usually measured by the dissolution test. The effect of excipients and the effect of the granulation process on the dissolution of tablets analyzed. The dissolution of tablets is a function of the granulation influence the bioavailability of the drug [90,91]. The dissolution process involves the disintegration of the dosage form in the dissolution medium during the test. This process is usually measured by the “dissolution” methods or through the use of predetermined time points. The dissolution profile of a dosage form is a function of the processing factors, excipients, and the granulation process. The dissolution method itself [90] and the references cited therein provide a detailed discussion of the dissolution methods.

### III. APPLICATION OF CHARACTERIZATION TO GRANULATION DESIGN

Characterization tools and methods, are most extensively used by the formulation scientist uses them to gain a better understanding of the granule and final product. The scientist as part of the design process uses these tools and techniques. The dry granulation is described by the processes that do not include the use of liquid. Though this is not a treatise on the use of these techniques in an optimization scheme, the selection of how these techniques are offered.



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(circles). (From Ref. 20.)

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disintegration time [89]. Nogami and co-workers explored the influence of the physicochemical properties of the penetrating solution on the disintegration of tablets [87]. They found that viscosity, surface tension, and contact angle of the penetrating solution influenced the disintegration of a tablet. The mean diameter of capillaries in the tablet (measured by air permeametry) were altered with compression force, and such effects on disintegration were evaluated. The authors determined that the Washburn equation of rate of penetration could be applied to the penetration of the solution into the tablet [87].

*b. Dissolution.* An assessment of the dissolution characteristics of the dosage form is usually made throughout the development of the product. The effect of excipients and processes on the dissolution profile are routinely analyzed. The dissolution of the drug substance from the dosage form can influence the bioavailability if the dissolution is rate-limiting for absorption [90,91]. The dissolution profile of a dosage form can be obtained by submersing the dosage form into the dissolution medium and agitating the medium during the test. This agitation can be achieved through "forced convection" methods or through sink methods [90]. The medium is sampled at predetermined time points and assayed for dissolved drug substance. The dissolution profile of a dosage form can be influenced by dosage form-processing factors, excipient, and drug substance factors, as well as by the dissolution method itself [9,31,90]. The reader is referred to these references and the references cited therein for more detailed information about dissolution methods.

### III. APPLICATION OF CHARACTERIZATION TECHNIQUES IN GRANULATION DEVELOPMENT

Characterization tools and techniques, as applied to granulation development, are most extensively used during the development of the process. The formulation scientist uses the techniques described in the foregoing sections to gain a better understanding of the relation between process parameters and granule and final product properties. This understanding is exploited by the scientist as part of the optimization of the process. In this section, the use of these tools and techniques for low shear, high shear, fluid bed, and dry granulation is described in detail. Low shear granulation includes those processes that do not include high-speed impeller or granulator motion. Although this is not a treatise in process optimization, these techniques can be used in an optimization scheme. At the conclusion of this section a description of how these techniques could be applied to process selection will be offered.

### A. Low Shear Granulation

Hydroxypropylmethylcellulose (HPMC) is a very useful excipient for controlling the release of a drug substance. Its poor flow properties, however, usually call for granulation methods to be put in place [92]. Recognizing that potential problems with gelling or overagglomeration in the presence of water could occur, Liu et al. addressed binder fluid (water) and nozzle size as process parameters and evaluated their effect on granule flow, size, density, and compressibility [92]. Water was sprayed, rather than poured, into a planetary mixer charged with either HPMC or a 1:1 mixture of HPMC and diclofenac sodium. By sieve analysis the geometric mean diameter increased with increasing binder fluid [92]. An increase in binder fluid and an increase in the nozzle diameter from 0.012 to 0.025 in. also improved the flowability of the granules, as determined by angle of repose measurements.

In addition, increases in both granule size and flowability were much more sensitive to nozzle diameter than binder fluid level [92]. Tablet hardness of the 1:1 mixtures decrease with increases in both parameters. Interestingly, the dissolution profiles of the 1:1 mixtures showed almost no sensitivity to either parameter. The authors concluded that the most desirable granule size was the lower size, and this could be achieved by using the smaller nozzle diameter. Balancing the loss in tablet hardness with the improvement in flowability could be achieved by selecting an optimal binder fluid level [92].

A wet granulation process can be quite sensitive to the ingoing starting material. Romero and co-workers studied the effect of different lots and suppliers of ibuprofen on the wet granulation process and subsequent tablet properties [93]. Lots of ibuprofen from different suppliers required different levels of binding fluid when wet granulated in a Hobart mixer. The bulk lots that had a smaller starting particle size required a greater amount of fluid. Moreover, the power consumption curves, although retaining the same basic shape between the larger-sized lots, were clearly different when compared with the smaller-sized lots [93]. The differences in final tablet quality were also evident. The hardness of tablets produced by wet granulation was higher for the smaller-sized material. Although this could be explained on the basis of bonding contact area alone, this illustrates the importance of working with starting materials that are consistent in their physical properties. A process developed with one set of materials could result in a final product of different quality, if those properties were allowed to vary. A similar example of the effect of particle size of the ingoing bulk drug on dosage form performance was also reported by Harwood and Pilpel for griseofulvin [16].

Cutt and co-workers investigated the influence of other physicochemical properties on those of granules [94]. Glass ballotini, with a starting

particle size of about 26- $\mu$ m, treating the beads with dimethylsiloxane with either hydrophilic (contact angle = 101°) starting materials or hydrophobized gelatin. Although the hydrophobicity of the surface was very sensitive to the same treatment, the hydrophobic glass were coated. The granules prepared from the hydrophobic glass were also noted.

A different approach to granulation, where the final product quality was more important than the work, dicalcium phosphate granules were used. Granule properties, such as flow, compaction, and tablet strength, were used to differentiate binders based on their efficiency. Efficiency is determined by the amount of input during the compaction process. This approach in separating the contribution toward compaction energy is that more compaction energy is required for recovery. More efficient binders are illustrated in Fig. 9. Here, the efficiency is determined to be more efficient than 4000 [95].

Wikberg and co-workers studied the effect of granules produced from wet granulation on the area under the air permeability curve, a factor of resistance to gas flow. The granules massed with ethanol-water had a higher permeability than when massed with water. The permeability of the tablet was also affected. The granules comprised granules that had a higher permeability during compaction [96]. The effect of granule porosity and permeability on tablet properties was also noted.

Chalmers and Elworthy studied the effect of various oxytetracycline granules on the wet-mixing time resulted in a higher permeability with mercury intrusion, and a higher permeability in bulk density. The strength of the granules and the intragranular porosity [97].

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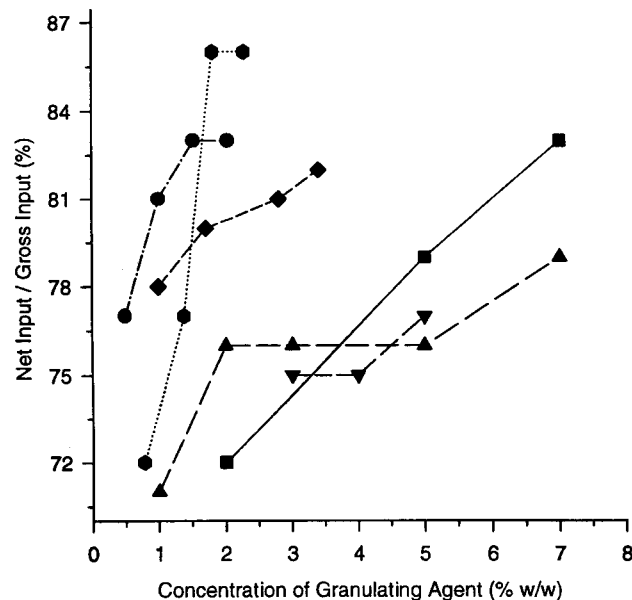
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Glass ballotini, with a starting

particle size of about 26–40  $\mu\text{m}$ , were deliberately made hydrophobic by treating the beads with dimethylsilane. A comparison of granules was made with either hydrophilic (contact angle =  $25^\circ$ ) or hydrophobic (contact angle =  $101^\circ$ ) starting materials wet granulated with either PVP, HPMC, or hydrolyzed gelatin. Although binder distribution was independent of the hydrophobicity of the surface, the resultant granule friability and strength were very sensitive to the same surface variable [94]. Granules prepared with the hydrophobic glass were considerably weaker and more friable than granules prepared from the hydrophilic glass [94]. Differences between the binders were also noted.

A different approach to evaluating the influence of various binders on final product quality was reported by Armstrong and Morton [95]. In their work, dicalcium phosphate dihydrate was wet granulated with various binders and water. Granule properties, such as crushing strength, and tablet compaction properties, such as net work of compaction, gross or total work of compaction, and tablet strength, were evaluated. The authors were able to differentiate binders based on their efficiency (Fig. 9). The estimate of efficiency is determined by taking the ratio of the net work input to total work input during the compaction of the granulation. This provides a normalized approach in separating the nonelastic contribution from the elastic contribution toward compaction energy [95]. Higher values of this ratio indicate that more compaction energy is applied to bonding, not reversible, elastic recovery. More efficient binders will exhibit steeper slopes of the curve illustrated in Fig. 9. Here, gelatin, wheat starch, and methyl cellulose were determined to be more efficient than PVP, acacia, or polyethylene glycol 4000 [95].

Wikberg and co-workers used air permeability of lactose tablets, produced from wet granulation, to differentiate binder solutions [96]. By using the area under the air permeability–compression pressure curve as an indicator of resistance to gas flow, they were able to demonstrate that granulations massed with ethanol–water mixtures produced tablets with greater permeability than when massed with the individual solvents. The higher permeability of the tablet was interpreted as a more porous entity which comprised granules that had a greater resistance to granule fragmentation during compaction [96]. This conclusion was supported with granule friability and granule porosity measurements [96].

Chalmers and Elworthy explored the effect of wet-mixing time on various oxytetracycline granule and tablet properties [97]. An increase in wet-mixing time resulted in a decrease in intragranular porosity, as measured with mercury intrusion, an increase in mean granule size, and an increase in bulk density. The strength of the granules was also inversely related to the intragranular porosity [97]. As shown in Fig. 10, both the disintegration

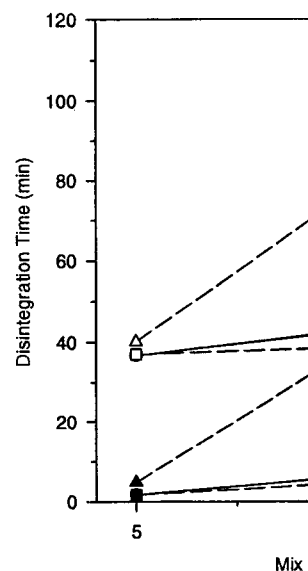


**Fig. 9** The relation between granulating agent concentration and the ratio of net work to gross work: More efficient granulating agents will exhibit a steeper slope: squares, PVP; upward triangles, acacia; downward triangles, polyethylene glycol 4000; diamonds, wheat starch; hexagons, gelatin; circles, methylcellulose. (From Ref. 95.)

time and  $T_{50\%}$  increased significantly with increasing mixing time, this effect becoming more enhanced when the particle size of the ingoing bulk drug was lower.

In a continuation of this work, Chalmers and Elworthy evaluated the effect of binder concentration and level on the resultant granule and tablet properties of oxytetracycline formulations [15]. In one part of this study, the level of PVP was kept constant and the concentration and amount of fluid were varied. As illustrated in Fig. 11, the differences in granule size were quite significant. The granules made with the highest volume of binder fluid were significantly larger, even though the overall amount of PVP was the same [15]. The authors suggest that the increase in volume increases the capillary cohesion of the mass and that this outweighs any increases in surface tension or viscosity with the higher concentration PVP solutions [15].

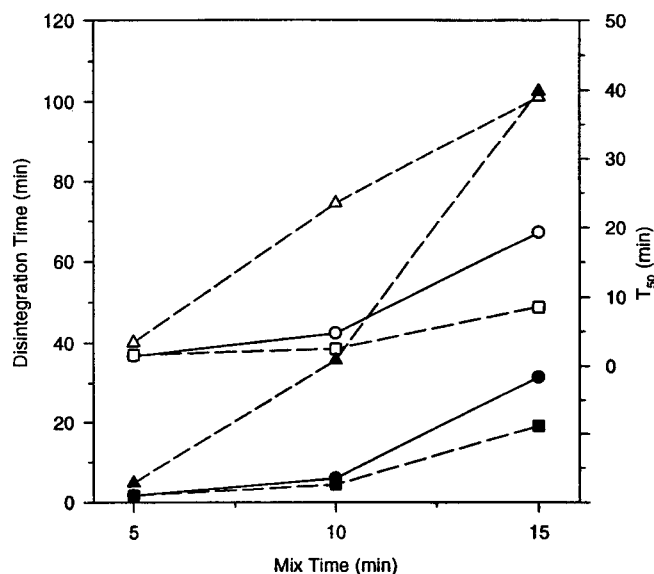
The trade-off for this process was improved tablet processing against reductions in dissolution rate [97]. A variation of this type of study was



**Fig. 10** Effect of varying properties of tablets comprised of granulation time; open symbols, 50-μm bulk; squares, 2.10-μm bulk; circles, 2.10-μm bulk.

reported by Akbuga [98]. The effect of binder concentration on the addition and wet-mixing time was also evaluated. Water, as the binder, was added in one bolus or added continuously. The continuous addition was slower during the continuous addition, which produced more agglomerates. This study emphasized the importance of not only the binder concentration but also the method of addition.

An interesting study on the effect of mixer type was reported by Hunter and Elworthy [99]. The effect of 45 μm) was wet granulated in a "Planetex" mixer of increasing size. The granules were evaluated for moisture content through a 12-mesh screen. The moisture content was then determined through a sieve cut was then determined. The moisture content increased with increasing mixer size, while the disintegration time decreased with increasing mixer size.

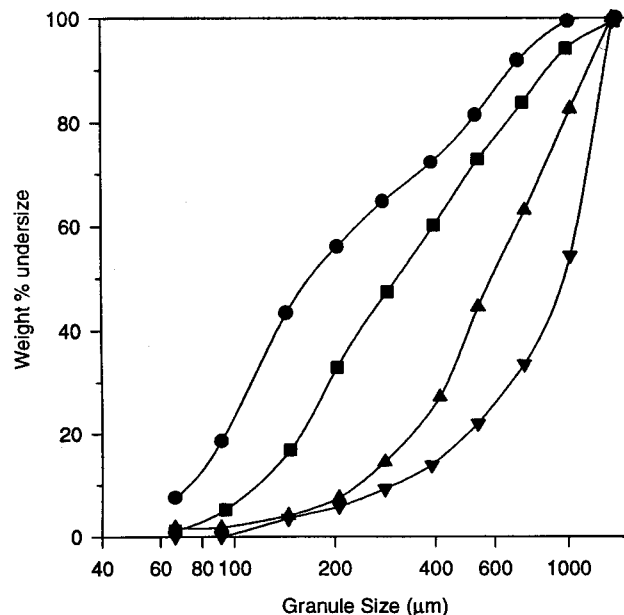


**Fig. 10** Effect of varying wet-mixing time on disintegration and dissolution properties of tablets comprised of oxytetracycline granulations: closed symbols, disintegration time; open symbols, dissolution time; triangles, 1.9- $\mu$ m bulk; circles, 15.0- $\mu$ m bulk; squares, 2.10- $\mu$ m bulk. (From Ref. 97.)

reported by Akbuga [98]. In this study the effect of method of binder fluid addition and wet-mixing time on the size of furosemide granules was evaluated. Water, as the binder fluid, was either added to a laboratory-scale mixer in one bolus or added continuously during mixing. Granule growth was slower during the continuous addition of water, although this process produced more agglomerates (granules > 2.0 mm) [98]. This study illustrated the importance of not only mixing time, but also the method of binder fluid addition.

An interesting study on scale effects for a planetary wet granulation was reported by Hunter and Ganderton [99]. Lactose BP (mean particle size, 45  $\mu$ m) was wet granulated with water as the binding fluid in three "Planetex" mixers of increasing capacity, 12, 60, and 200 kg. Samples from various positions in the bowls were taken during the wet-mixing phase and evaluated for moisture content. The samples were also dried and pushed through a 12-mesh screen. The intragranular porosity of the -12+16 mesh sieve cut was then determined [99]. The spatial variation in moisture content increased with increasing mixer size [99]. Although the intragranular porosity decreased with increasing mixing times, the intragranular porosity also

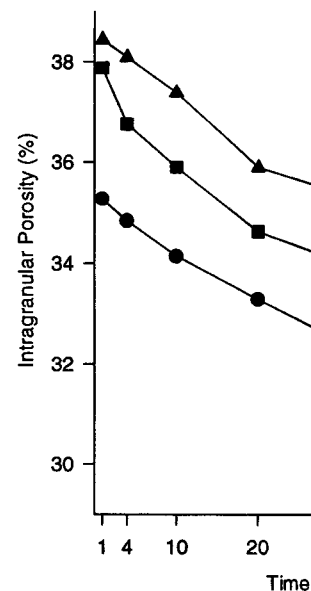




**Fig. 11** The effect of varying the amount of binder solution added to the oxytetracycline formulation, with the PVP content constant, on the granule size distribution. Volume and concentration of PVP solution added: circles, 21.0% v/w, 3.57% w/v; squares, 30.0% v/w, 2.5% w/v; upward triangles, 39.0% v/w, 1.92% w/v; downward triangles, 45.0% v/w, 1.67% w/v. (From Ref. 15.)

decreased with increasing scale (Fig. 12). The authors hypothesized that the more dense granules that were produced at the larger scale were subjected to higher forces as the mass was swept upward by the mixing blade [99]. The important point to be made from this work is that if the development of a wet granulation process is completed in the laboratory, sufficient attention should be paid toward potential scale differences. If, for example, it was unclear that lower intragranular porosity could negatively affect the performance of the final dosage form, the formulation scientist could wet mix even longer at the smaller scale to ascertain potential negative scale effects.

Opankunle and co-workers studied the effect of granule size and density on the rate of granule drying [100]. Granules containing either lactose or sulfathiazole were wet massed in a Glen mixer with acacia mucilage or povidone and pushed through an 8-mesh screen. The moisture content was determined using an LOD measurement and a known quantity of the gran-



**Fig. 12** The mean intragranular porosity (%) versus time for granules produced in "Beken" mixers: tr kg scale. (From Ref. 99.)

ulation placed in a control weighing system. The loss determined using this apparatus particle size and volume distribution the determination of granules created by using greater a drying rate of granules decreased increasing granule density and Ganderton, the formula of Opankunle et al. and mulations as they are transferred

## B. High Shear Granulation

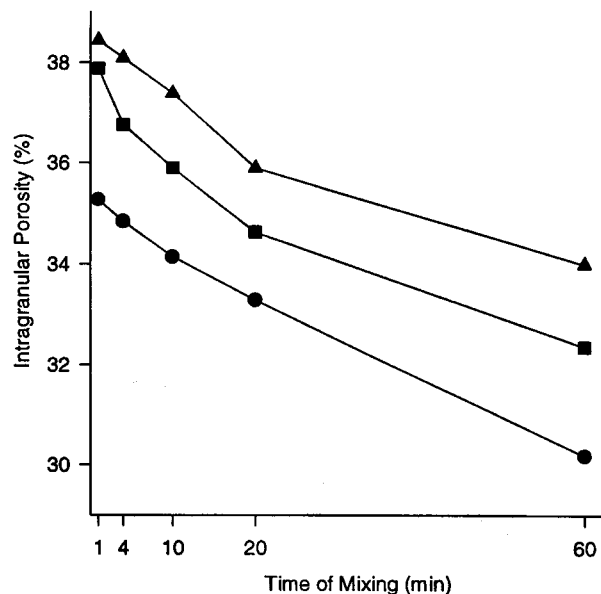
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**Fig. 12** The mean intragranular porosity of -12+16-mesh lactose granules produced in "Beken" mixers: triangles, 12-kg scale; squares, 60-kg scale; circles, 200-kg scale. (From Ref. 99.)

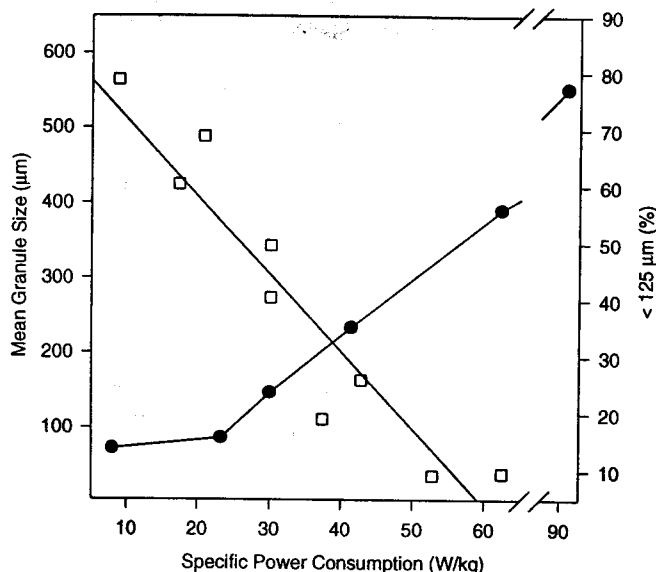
ulation placed in a controlled, forced hot air oven that was equipped with a weighing system. The loss of moisture during drying was directly determined using this apparatus. Sieve analysis was used to characterize the particle size and volume displacement of the granules, and xylene was used in the determination of granule density. Larger and denser granules were generated by using greater amounts of water during granulation [100]. The drying rate of granules decreased with increasing average granule size and increasing granule density [100]. Given the scale effects described by Hunter and Ganderton, the formulation scientist could capitalize on the observations of Opankunle et al. and more effectively define the drying cycles of granulations as they are transferred up in scale [99,100].

## B. High Shear Granulation

Process development in a high shear granulation has been extensively reviewed in the pharmaceutical literature. The reason may have to do with the number of process parameters that can be used to modify the properties of the granulation and final product. Impeller speed, granulator (chopper)

speed, binder fluid addition rate, binder fluid level, and kneading or wet-mixing time, all can be adjusted to alter the properties of the granule.

An example of the effects of binder fluid addition method was offered by Timko and co-workers [101]. A lactose-microcrystalline cellulose blend was wet granulated in a high shear mixer with povidone as the binder. The power consumption during granulation was monitored using a motor load analyzer [101]. Power consumption increased when the binder, a 5% w/w povidone-water system, was dumped in, rather than sprayed. The power consumption was reduced when the chopper was used during binding fluid addition [101]. However, the motor load analyzer could not detect differences between the method of addition of povidone (e.g., as part of the dry blend or in the binder fluid). Holm et al. performed a similar study with a Fielder PMAT 25 (Fielder, UK) fitted with an Elfi G2 power consumption meter [102]. The authors were unable to correlate both the increase in mean granule size and the loss of fines in a lactose-PVP-PVA granulation to the specific power consumption. An example of the data is shown in Fig. 13 [102].



**Fig. 13** Correlation between specific power consumption, mean granule size, and percentage fines for a lactose granulation in a high shear mixer: chopper speed, 3000 rpm; impeller speed, 250 rpm; closed symbols, mean granule size; open symbols, percentage fines. (From Ref. 102.)

Similar to planetary mixing, granulation is also an important process. The authors explored the effect of this process on numerous physical properties of a sucrose-lactose-starch-based granule with water in a Littleford-Labette (PA) and fluid bed dried in a Fluid Bed Dryer (zerland). By using a starch-based binder, the mixing time was evaluated and compared in the granule size distribution. The results by sieve analysis, disappearance of fines, resulted in a similar sensitivity to mixing time.

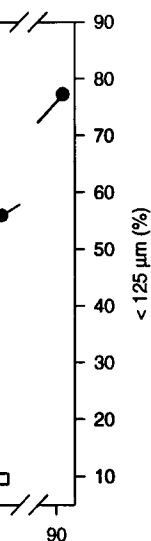
Schaefer and co-workers [103] studied mixing time and the influence of impeller properties [103]. Although they observed a decrease in mixing time with impeller speed, they also observed a decrease in granule size with peller speed [34]. This process was studied although the sensitivity was not. Interestingly, adhesion of the wet granules to the endpoint from being mounted on the impeller [103] was not a problem if this type of analysis was used for shear wet granulation process.

The amount of binder fluid added is critical for high shear granulation. The effect of binder fluid level, wet-mass, and properties of an  $\alpha$ -lactose monohydrate were studied. The granulator used in this study was a Fielder PMAT 25, Fielder, UK). The effect of the fragmentation of granules was studied with mercury pycnometry, with a 10% fines level [30]. The granules with the highest fines had the highest granulation propensity. The effect of impeller speed, on this process, was studied. The conclusion from these studies was that the amount of binder fluid used to alter the compaction of the granules was critical.

In a study that probed the effect of processing conditions (Luca, Italy) that affected product quality, the standard deviation, using

fluid level, and kneading or wet-mixing properties of the granule.

fluid addition method was offered for a microcrystalline cellulose blend with povidone as the binder. The process was monitored using a motor load analyzer when the binder, a 5% w/w solution, was added rather than sprayed. The power consumption was used during binding fluid addition. The analyzer could not detect differences in povidone (e.g., as part of the dry blend). A similar study was performed with a 5% w/w starch-PVP-PVA granulation to the effect of the data is shown in Fig. 13.



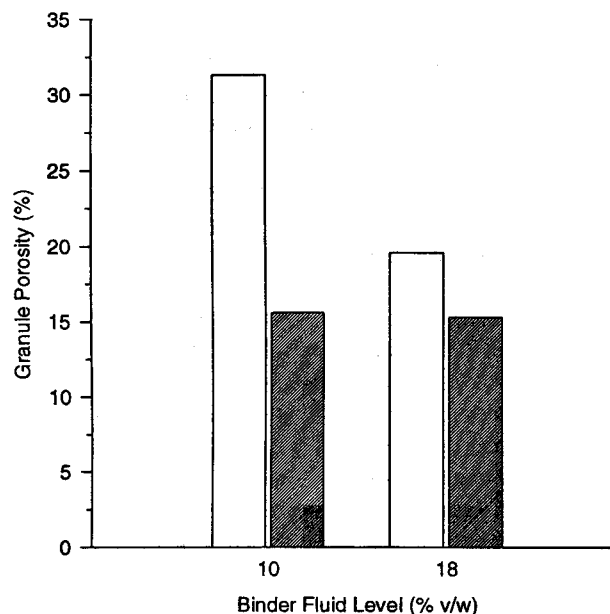
consumption, mean granule size, and high shear mixer: chopper speed, 3000 rpm; mean granule size; open symbols,

Similar to planetary mixer wet granulations, mixing or kneading time is also an important process parameter in high shear granulation. Ertel et al. explored the effect of this process variable, as well as scale of mixing, on numerous physical properties of the granulation and tablet [34]. In this study sucrose-lactose-starch-based granulations of dyphylline were wet massed with water in a Littleford-Lodge mixer. The mass was then passed through a Stokes oscillating granulator (F.J. Stokes Machine Company, Philadelphia PA) and fluid bed dried in an Aeromatic dryer (Aeromatic AG, Basel, Switzerland). By using a starch paste binder, the effect of postbinder addition mixing time was evaluated at both the 4- and 30-kg scale [34]. Differences in the granule size distributions between the scales of mixing, as determined by sieve analysis, disappeared at the longer times [34]. Mixing at both scales resulted in a similar sensitivity of the dissolution rate of the drug to mixing time.

Schaefer and co-workers also elevated both the influence of wet-mixing time and the influence of ingoing material on various granule properties [103]. Although they observed trends similar to those of Ertel et al., they also observed a decrease in intragranular porosity with increasing impeller speed [34]. This property was also sensitive to the chopper speed, although the sensitivity was minimized at high impeller speeds [103]. Interestingly, adhesion of the wet mass to the sides of the mixing bowl prevented the endpoint from being accurately determined from a load analyzer mounted on the impeller [103]. The reader should be aware of this complication if this type of analysis is being used in the development of a high shear wet granulation process.

The amount of binder fluid during wet massing has also been studied for high shear granulation. Wikberg and Alderborn studied the effects of binder fluid level, wet-massing time, and main impeller speed on the properties of an  $\alpha$ -lactose monohydrate-polyvinyl pyrrolidone granulation [30]. The granulator used in this study was a 25-L high shear mixer (Fielder PMAT 25, Fielder, UK). The authors were able to correlate granule porosity with the fragmentation of granules during compaction, when using air and mercury pycnometry, with an air permeability technique, on intact tablets [30]. The granules with the highest porosity exhibited the highest fragmentation propensity. The effect of process parameters, such as binder fluid level and impeller speed, on this property is illustrated in Fig. 14 [30]. The conclusion from these studies was that high shear process parameters could be used to alter the compaction characteristics of the granulation [30].

In a study that probed similar process variables, Vojnovic et al. explored processing conditions on a Zanchetta Roto J granulator (Zanchetta, Luca, Italy) that affected properties; such as mean granule size and geometric standard deviation, using sieve analysis; granule compressibility, using



**Fig. 14** Primary and volume reductions in lactose granulations: open bars, impeller speed 250 rpm; filled bars, impeller speed 500 rpm. (From Ref. 30.)

tapped and untapped density; and flow rate, using flow through an orifice [104]. A lactose–cornstarch blend was granulated with water and polyvinyl pyrrolidone. The process parameters included moisture level, impeller speed, and granulation time [104]. With use of a central composite design, the authors determined that (a) moisture level influenced granule size and flow rate; (b) impeller speed influenced granule size, standard deviation, and compressibility; (c) granulation time influenced compressibility. With this information they were able to produce granulations with individual optimal properties and, in a later publication, one granulation with all properties optimized [104,105].

The use of response surface methodology and statistical design is an effective way of incorporating a characterization scheme into granulation process development. Typical examples for high shear granulation development include those described in the foregoing as well as work reported by Holm et al. and Wehrlé et al. [104–107]. With a Fielder-PMAT 25 high shear mixer, Holm et al. explored the effect of the binder fluid addition method (two levels), binder fluid addition rate (two levels), impeller speed (two levels), and chopper speed (two levels) on the appearance of agglom-

erates and homogeneity of [106]. By ANOVA, the authors determined the effect of impeller speed, chopper speed, and binder fluid level on the appearance of large granules. The authors found that chopper speed and addition rate were significant factors, while binder fluid level was not significant. The authors also found that the addition rate, binder fluid level, and chopper speed were significant factors in determining granule size, fluid addition rate, and granule size [106].

Wehrlé et al. used response surface methodology to study the effect of granule size, but also other properties such as hardness, and disintegration time. The material was wet granulated in a Turbula mixer. The parameters tested were binder fluid level, impeller speed, and chopper speed. The authors found that the analysis of variance was optimal for granule size and hardness. The authors also found that these two parameters were significant factors. The authors also found that the analysis of variance was validated by the authors.

The usefulness of granulation process development and shear granulation process has been evaluated by Sinko and co-workers evaluated binder fluid level, granule size and intragranular porosity, and granule size [108]. The batch size ranged from 100 to 200 g. The authors shifted both properties. A decrease in granule size was observed with an increase in granule size obtained on a Diosna Mixer. The authors interpreted this increase as a result of compaction in the larger mixer. The authors also found that the impeller blade, and motor speed, and mixing [108]. Similar results were observed in a particular report is an excellent example of the scale-up of a high shear granulation process.

Horsthuis and co-workers studied the effect of granulation in a Gral mixer (Mettler). The range in this study was 2.6–10.0 g. The authors found that the point at which the granule size no longer changed. The authors also found that the ratio of the centrifugal force to the tangential force was a “criterion for determining the granule size number requires the impeller speed to be constant. This parameter was found to be independent of impeller tip speed. At least one factor was superior to tip speed in determining granulation process (Fig. 16).

erates and homogeneity of residual moisture of lactose-PVP granulations [106]. By ANOVA, the authors found that at lower moisture contents impeller speed, chopper speed, and addition method had a significant influence on the appearance of large agglomerates. Although similar sensitivity to chopper speed and addition method were observed at higher moisture contents, fluid addition rate, rather than impeller speed, was more significant [106].

Wehrlé et al. used response surface methodology to optimize not only granule size, but also other tablet parameters, such as ejection force, tablet hardness, and disintegration time [107]. A lactose-cornstarch-PVP blend was wet granulated in a Turbosphère TS10 (Moritz, France). The process parameters tested were binder fluid level and mixing time [107]. From this analysis optimal granule and tablet properties were obtained by adjusting these two parameters. The optimal processes parameters were subsequently validated by the authors.

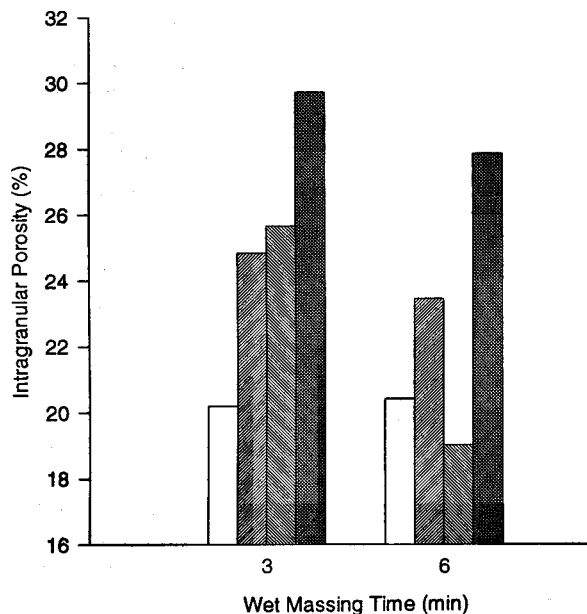
The usefulness of granulation characterization in the scale-up of a high shear granulation process has also been reported in the literature. Schaefer and co-workers evaluated both scale and type of high shear mixer on the size and intragranular porosity of a dicalcium phosphate-based granulation [108]. The batch size range was 10–100 kg. Granulation in larger mixers shifted both properties. A decrease in both intragranular porosity and mean granule size was observed with increasing mixer size; Fig. 15 shows data obtained on a Diosna Mixer (Dierks & Sohne, Germany) [108]. The authors interpreted this increase as a result of a decrease in the efficiency of granule compaction in the larger mixers. Compaction, the authors explain, occurs at the impeller blade, and more product will see the impeller blade during mixing [108]. Similar results were also observed for Fielder mixers. This particular report is an excellent starting point for information relating to the scale-up of a high shear granulation process.

Horsthuis and co-workers studied the scale-up of a lactose-based granulation in a Gral mixer (Machines Collette, Belgium) [109]. The batch size range in this study was 2.6–100 kg. The endpoint was defined as the time point at which the granule size distribution, as determined by sieve analysis, no longer changed. The authors characterized the various scales of mixers using a *Froude number* [109]. This dimensionless number is defined as the ratio of the centrifugal force to the gravitational force and was used in this study as a “criterion for dynamic similarity” between mixers [109]. The number requires the impeller speed, impeller diameter, and the gravitational constant. This parameter was compared with a traditional scale parameter, impeller tip speed. At least for this type of mixer, the Froude number was superior to tip speed in defining the effect of scale on the endpoint of the granulation process (Fig. 16) [109].

lactose granulations: open bars, impeller  
rpm. (From Ref. 30.)

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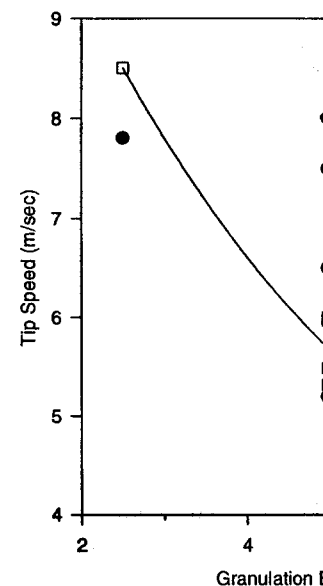


**Fig. 15** Effect of wet-massing time on intragranular porosity of dicalcium phosphate granulations in Diosna mixers: open bars, Diosna P25 with standard tools; upward right-hatched bars, Diosna P50; upward left-hatched bars, Diosna P25 with special tools; dotted bars, Diosna P250. (From Ref. 108.)

### C. Fluid Bed Granulation

Similar to the literature on high shear granulation, the literature on fluidized bed granulation, or fluid bed granulation, is replete with examples of process variables and their effects on final product quality. A good starting point for the scientist is a chronologic review of the field by Banks and Aulton [110]. In this section some examples of granulation characterization as applied to fluid bed product development are also reviewed.

Andreev et al. used sieve analysis to propose a mechanism for granule growth in a fluid bed granulator [111]. Amidopyrine (aminopyrine) was granulated with an aqueous methylcellulose solution in an Aeromatic (Aeromatic AG, Switzerland) with atomization time as the process variable that was evaluated. With the binder solution rate set constant, the atomization, or addition, time was varied between 3 and 36 min [111]. The mean granule diameter increased up to a certain point and then decreased slightly as well as widened. Eventually, the mean diameter would increase again with increasing atomization time. By plotting the weight percentage of granules of

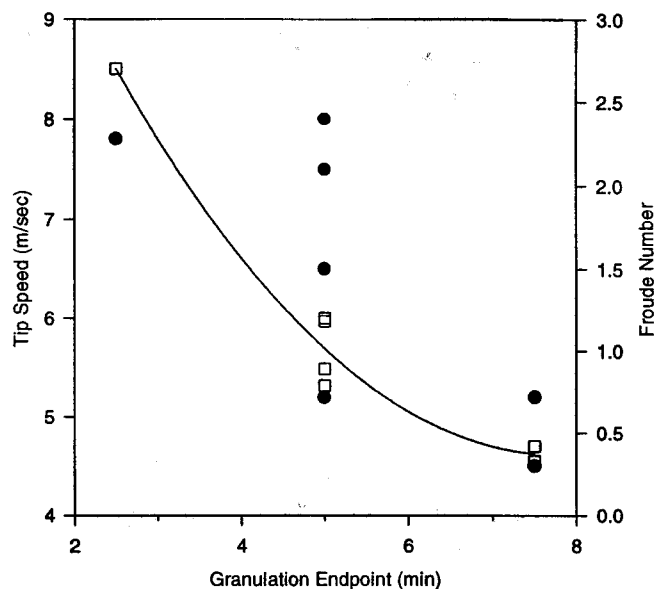


**Fig. 16** Tip speed and Froude number versus granulation time demonstrates a more uniform granulation process. Tip speed: circles, tip speed; square, Froude number.

certain sized fractions versus granulation time, the authors found a biphasic curve with a maximum at 17 min [111]. The authors interpreted this as a switch from primary granulation to secondary granulation, where granules that form larger agglomerates.

Alkan and Yuksel also studied the effect of granulation time on granule growth mechanism for a large-scale granulation process [112]. They made a comparison of granule growth relative to the shift in granule size distribution. They found that granule friability leveled to a constant value after 17 min. They proposed two mechanisms of granule growth: one mechanism that is predominant in the initial granulation mechanism that is predominant in the later granulation mechanism.

Ormós and co-workers studied the effect of granulation time on the size growth as well as the granule strength of granules granulated with aqueous gelatin solution. They found that the amount of product that



**Fig. 16** Tip speed and Froude number as a function of endpoint. The line drawn demonstrates a more uniform correlation of Froude number to endpoint than tip speed: circles, tip speed; squares, Froude number. (From Ref. 109.)

granular porosity of dicalcium phosphates, Diosna P25 with standard tools; left-hatched bars, Diosna P25 with

ulation, the literature on fluidized bed granulation is replete with examples of process variability. A good starting point for a review of this field by Banks and Aulton [110]. The application of granulation characterization as applied to fluidized bed granulation is reviewed.

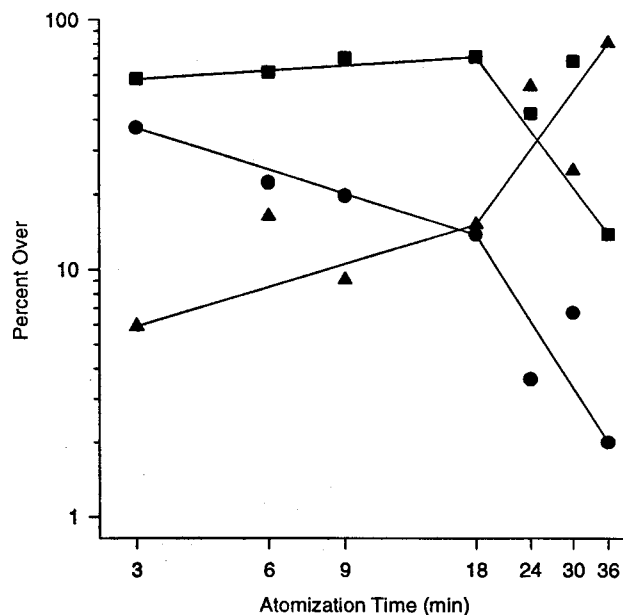
propose a mechanism for granule growth. In the case of Amidopyrine (aminopyrine) was granulated in an Aeromatic (Aeromatic) solution in an Aeromatic (Aeromatic) time as the process variable that was set constant, the atomization, was 36 min [111]. The mean granule size then decreased slightly as well as the wear resistance would increase again with increasing weight percentage of granules of

certain sized fractions versus atomization time on a log-log plot, the authors found a biphasic curve with an identical transition for all size fractions (Fig. 17) [111]. The authors interpreted this transition as one that occurs with a switch from primary granule growth by binder adhesion to a coalescence of granules that form larger agglomerates [111].

Alkan and Yuksel also suggested that there is a transition in the granule growth mechanism for a lactose-starch system wet granulated with a PVP solution [112]. They made observations similar to those of Andreev et al. relative to the shift in granule size distribution at this transition and also found that granule friability, which was decreasing before this transition, leveled to a constant value above this transition [111,112]. The authors proposed two mechanisms of large agglomerate growth: a "snowballing" mechanism that is predominant before the transition, and a granular aggregation mechanism that is predominant after this transition [112].

Ormós and co-workers evaluated both binder level and feed rate on the size growth as well as the wear resistance of quartz sand that was granulated with aqueous gelatin solution [113]. Wear resistance was defined as the amount of product that was retained on a 400- $\mu$ m sieve after it was





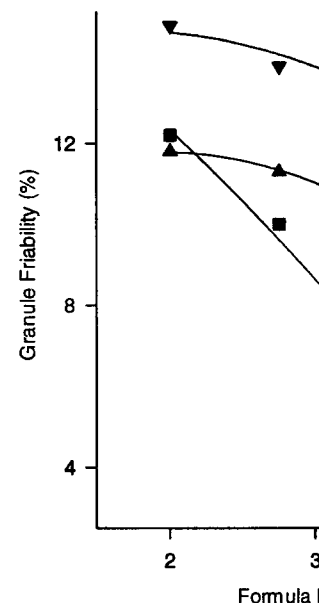
**Fig. 17** The relation between percentage retained and atomization time for the growth of aminopyrine (amidopyrine) granules in a fluid bed granulator. A characteristic shift in granule growth mechanism is observed at 18 min: triangles, 141- to 2.45-mm-sized fraction; squares, 0.28- to 0.71-mm-sized fraction; circles, 0.05- to 0.22-mm-sized fraction. (From Ref. 111.)

subjected to fluidization in a 4-cm glass apparatus. The addition of greater amounts of binder, either through increased solution concentration or lengthened spray time, strengthened the granules and reduced their wear resistance [113]. No differences between solution concentration and spray time were observed. In a subsequent study, increasing the solution feed rate resulted in granules with less wear resistance [114]. Average granule size also decreased slightly with a greater decrease at higher solution volumes. The distribution of binder across granule sizes was quite dependent on the feed rate, particularly for the smaller granules [114].

In a series of published reports Davies and Gloor evaluated the influence of both composition and fluid bed process parameters on the size, friability, flowability, and density of a lactose-cornstarch mixture [115,116]. Granule flowability was determined using a flow through an orifice-type design, and sieve analysis was used in the determination of granule size. Process parameters, such as increasing binder feed rate and decreasing inlet

air temperature, increased the granule size. Granule size was correlated with an increase in inlet air pressure and decreasing nozzle diameter. Granule size, density, and flowability, although both parameters were not measured, were similar in these authors' study. These authors reported similar properties of granules prepared by different methods. The effects are reported in Figs. 16 and 17. The granulation time. These types of granules are used in the characterization program in the development of a granulation development which, in real

Higashide and co-workers [117] studied the effect of the genericity of 5-fluorouracil (5-FU) in a fluid bed granulator [117]. The granule size of hydroxypropylcellulose in granules decreased with increasing granule size to the target potency [117]. The granule size varied in the exact same manner



**Fig. 18** Plot of the lactose-cornstarch formula binder weight: squares, lactose-cornstarch; downward triangles, acacia; circles, lactose-cornstarch; upward triangles, acacia.



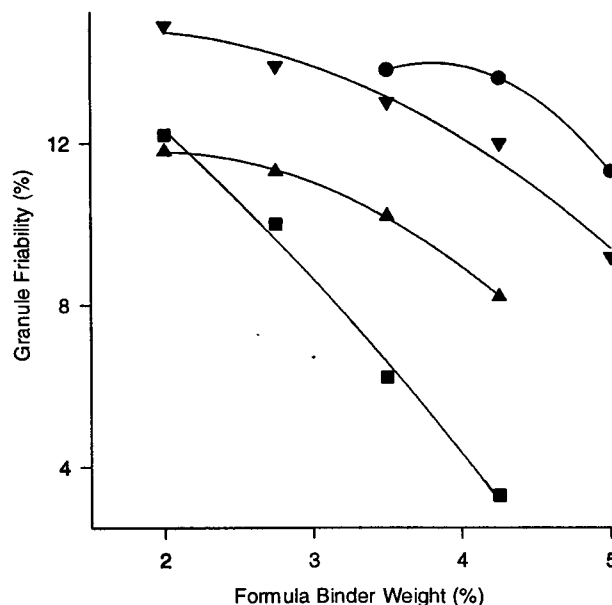
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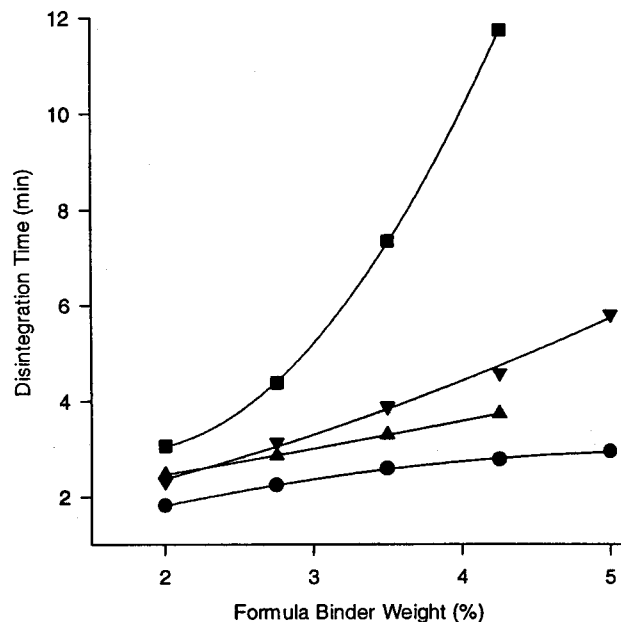
s and Gloor evaluated the influ-  
process parameters on the size,  
e-cornstarch mixture [115,116].  
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air temperature, increased the flowability of the granulation [115]. This trend was correlated with an increase in average granule size. Increasing air pressure and decreasing nozzle height resulted in almost no change in flowability, although both parameters increased average granule size [115]. In a similar study these authors evaluated the effect of various binders on the properties of granules prepared by fluid bed granulation [116]. Typical effects are reported in Figs. 18 and 19 for granule friability and tablet disintegration time. These types of studies illustrate the importance of a characterization program in the combination of composition selection and process development which, in reality, must go hand in hand.

Higashide and co-workers investigated the causes behind the inhomogeneity of 5-fluorouracil (5-FU) as a function of granule size when prepared in a fluid bed granulator [117]. With lactose and starch as inert fillers and hydroxypropylcellulose in water as the binder, the concentration of 5-FU decreased with increasing granule size to a minimum and then increased up to the target potency [117]. With a precipitation method, the starch content varied in the exact same manner, thereby leading to the conclusion that the



**Fig. 18** Plot of the lactose-starch granule friability relative to various binders and formula binder weight: squares, hydroxypropylcellulose; upward triangles, gelatin; downward triangles, acacia; circles, povidone. (From Ref. 116.)



**Fig. 19** Plot of the lactose–starch tablet disintegration time comprised of lactose–starch granules relative to various binders and formula binder weights: squares, hydroxypropylcellulose; downward triangles, acacia; upward triangles, gelatin; circles, povidone. (From Ref. 116.)

drug has an affinity for starch. As a result the authors were able to more evenly distribute the drug by balancing the starch and lactose level in the granulation [117]. This example illustrates the importance of other, non-physical methods for characterizing granulations in an attempt to better control the wet granulation process.

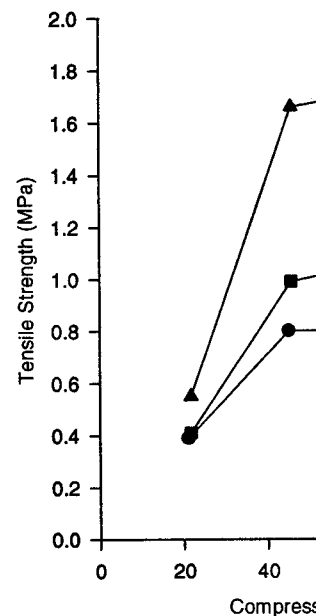
Numerous examples of characterization studies that incorporate experimental design for fluid bed granulation can be found in the literature. Many process parameters can be moved systematically to ascertain optimal processing conditions. Examples of this type of approach have been offered by Lipps and Sakr as well as by Meshali et al. [11,118].

#### D. Dry Granulation

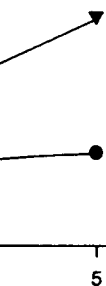
Many of the techniques described in the foregoing for wet granulation can also be applied to the dry granulation of powder. Malkowska and Khan explored the well-known reworking phenomenon by evaluating the recom-

pression characteristics of the recompression behavior of cellulose, and dicalcium phosphate under various initial compression forces, and the initial size of the granules for recompression. An example is shown in Fig. 20 for direct compression. The results are considerably weaker [119]. This can be explained as a manifestation of the reworking phenomenon.

Hervieu and co-workers [120] studied the effect of process parameters, such as the flowability and compressibility, on the maximum tablet hardness to be achieved. They found a similar loss in granulation strength with Malkowska and Khan's results.



**Fig. 20** The effect of recompression on the tensile strength profiles of direct compression tablets. (From Ref. 119.)



egration time comprised of lactose-  
formula binder weights: squares, hy-  
dia; upward triangles, gelatin; circles,

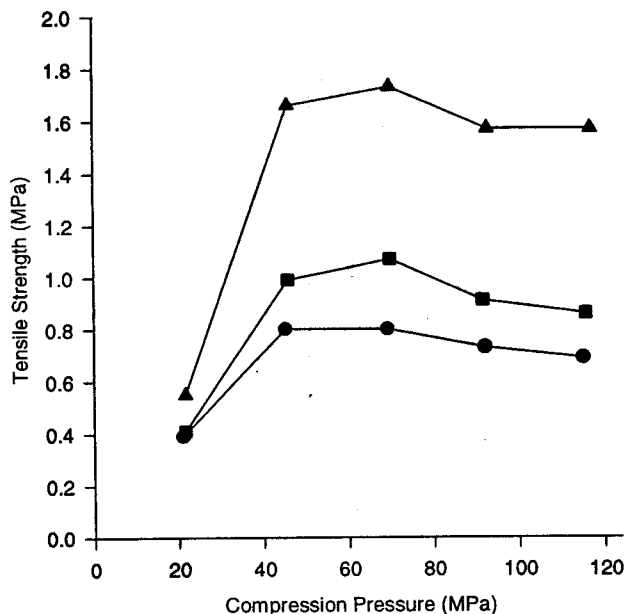
t the authors were able to more  
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regoing for wet granulation can  
powder. Malkowska and Khan  
menon by evaluating the recom-

pression characteristics of slugged excipients [119]. The authors evaluated the recompression behavior of direct compression starch, microcrystalline cellulose, and dicalcium phosphate dihydrate by preparing slugs compressed under various initial compression pressures. The slugs were then milled and sieved, and the initial size fraction (of the original material) was retained for recompression. An example of the reworking phenomenon is illustrated in Fig. 20 for direct compression of starch. The reworked tablets were considerably weaker [119]. The authors concluded that this phenomenon could be explained as a manifestation of "cold working" or hardening [119].

Hervieu and co-workers evaluated the effect of the roller compaction process parameters, such as feed rate, roller speed, and roller pressure, on the flowability and compressibility of an experimental powder system [120]. Compressibility was determined using a "cohesion index"—the ratio of the maximum tablet hardness to the maximum punch pressure [120]. They found a similar loss in granulation compressibility on recompression, in agreement with Malkowska and Khan and observed that this loss was sensitive to both

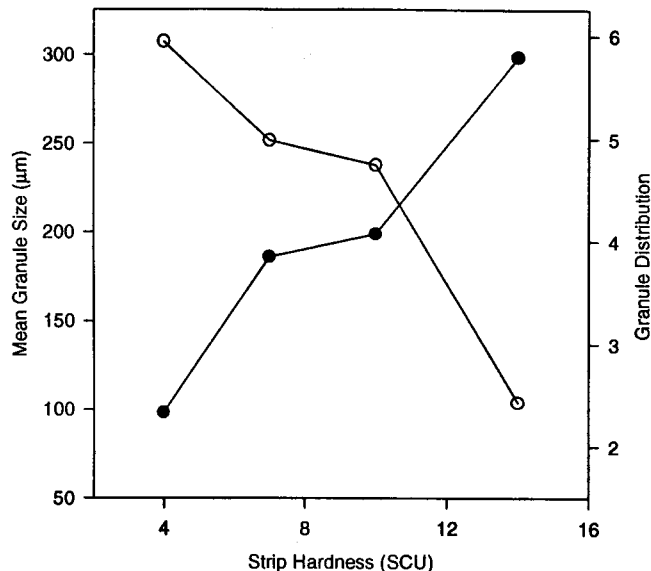


**Fig. 20** The effect of recompression on the tensile strength compression pressure profiles of direct compression starch at a dwell time of 15 s: triangles, first compression; squares, recompressed (first at 23 MPa); circles, recompressed (first at 70 MPa). (From Ref. 119.)

the feed rate and the roller speed [119]. The authors cited the ratio of the roller speed to the feed speed as a better indicator of the recompressibility problem than the individual rates [120].

Jaminet and Hess proposed a hardness test for roller-compacted materials [121]. The briquettes, or strips, were placed in a three-point, flexure tester (one point on top of the strip in the middle and the other points on the bottom near both ends). The hardness of the strip is obtained when the one point on top is moved in to break the sample [121]. The authors used this to evaluate the effectiveness of powder binders in a lactose–wheat starch system. A relation between strip hardness and both granule size and distribution was found (Fig. 21). This type of test can be used as a quick way of adjusting process parameters to obtain desired product quality such as particle size.

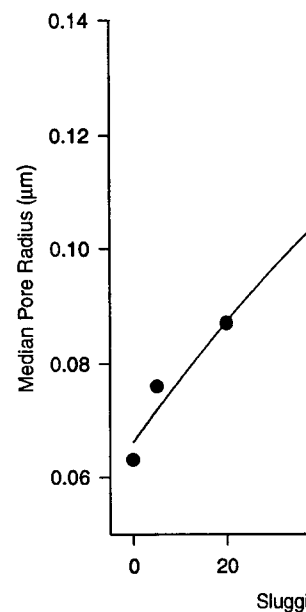
In a study reported by Kawashima and co-workers, the effect of slugging pressure on the sustained release of acetaminophen from hydroxypropylcellulose (HPC) matrices was explored [122]. The dissolution time ( $T_{50}$ ) and disintegration time of tablets prepared from slugged acetaminophen–HPC granules decreased with increasing slugging pressure. The swelling



**Fig. 21** Effect of binder content on strip hardness and its influence on mean granule size and distribution: closed symbols, mean granule size; open symbols, granule size distribution (standard deviation). (From Ref. 121.)

force of the tablets was also measured using a filter and a load cell. When the tablet swelled and generated a force, the load cell [122]. Over time, the pressures generated a greater force as the tablets disintegrated.

The authors explained the differences in the intergranular forces. They evaluated the pore structure of the granules and found the trends that higher-slugging pressures resulted in greater pore sizes. They reasoned that the greater pore sizes resulted in greater initial swelling [122]. The force of granules: The initial swelling at long time intervals, the same value (Fig. 23). This type of characterization, by both methods, can help explain and optimize the process.

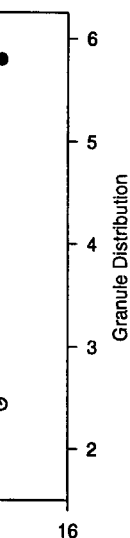


**Fig. 22** Mean pore radius of acetaminophen granules prepared by v

the authors cited the ratio of the indicator of the recompressibility

test for roller-compacted material placed in a three-point, flexure middle and the other points on of the strip is obtained when the sample [121]. The authors used binders in a lactose–wheat starch and both granule size and distribution can be used as a quick way of desired product quality such as

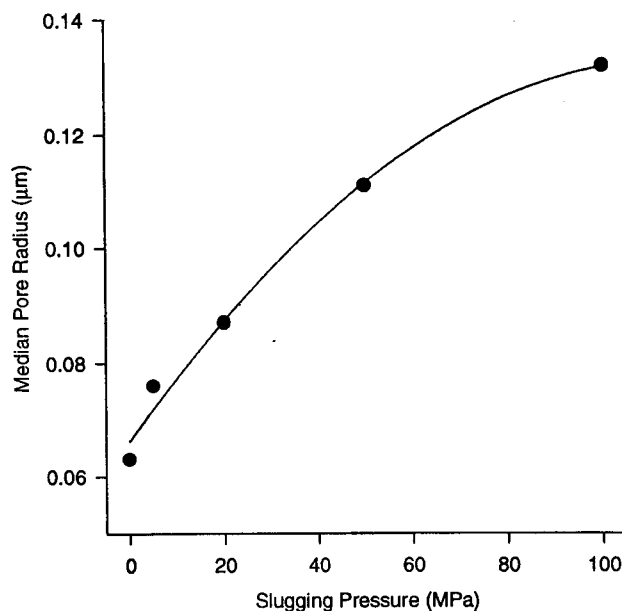
and co-workers, the effect of slugging acetaminophen from hydroxypropyl [122]. The dissolution time ( $T_{50}$ ) from slugged acetaminophen–slugging pressure. The swelling



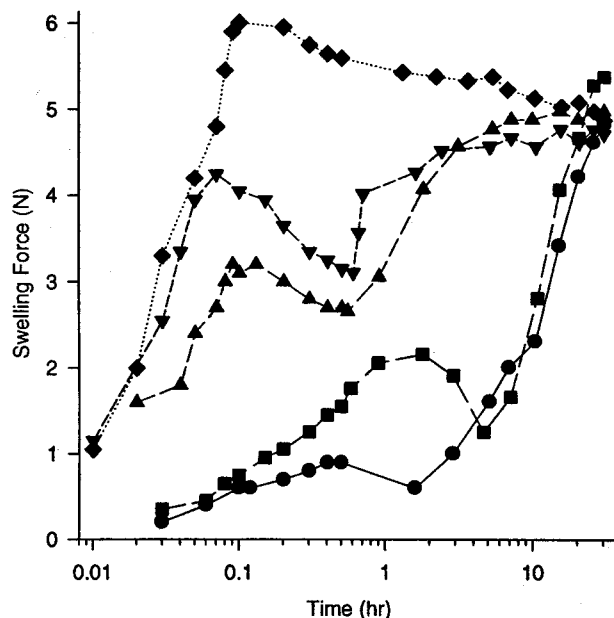
ess and its influence on mean granule size; open symbols, granule [121.]

force of the tablets was also measured by placing the tablet between a glass filter and a load cell. When water penetrated the tablet through the filter, the tablet swelled and generate an opposing force that was recorded by the load cell [122]. Over time, the tablets prepared with granules slugged at higher pressures generated a greater initial swelling force and then a reduction in this force as the tablets disintegrated.

The authors explained that this greater rate of swelling was caused by the differences in the internal pore structure of the individual granules [122]. They evaluated the pore structure of the granules using mercury porosimetry and found the trends that are reported in Fig. 22. Granules produced with higher-slugging pressures had a greater mean pore radius. The authors reasoned that the greater pore radius permitted faster water penetration; hence, greater initial swelling [122]. To confirm this, they evaluated the swelling force of granules: The individual granules exhibited this behavior, although at long time intervals, the force generated for all granules converged to the same value (Fig. 23). This type of study is a good illustration of how granule characterization, by both mercury porosimetry and swelling, can be used to help explain and optimize an overall tablet property: the dissolution time.



**Fig. 22** Mean pore radius of tablets produced from slugged HPMC–acetaminophen granules prepared by various slugging pressures. (From Ref. 122.)



**Fig. 23** Swelling force profiles of admixtures of slugged HPMC and acetaminophen (circles) and slugged HPMC-acetaminophen granules: squares, 5 MPa; upward triangles, 20 MPa; downward triangles, 50 MPa; diamonds, 100 MPa. (From Ref. 122.)

### E. Characterization for Process Selection

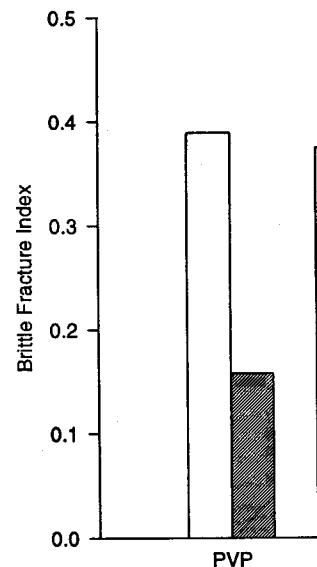
The formulation scientist has many processing options to choose from when granulation is needed. Characterization is an important component of the selection process. In this section, examples of characterization in the comparison of processes are drawn from the literature. These examples can be separated into two broad categories. The first would be direct compression versus granulation, the second being a comparison of various granulation processes (low shear versus fluid bed, and such). The first category addresses the questions alluded to at the beginning of this chapter; namely, which characteristics of a powder system can be modified or improved with wet granulation?

Itiola and Pilpel reported that metronidazole was a difficult compound to compress in a direct compression formulation because it was prone to capping [123]. They compared the tableting characteristics of formulations containing up to 56% w/w of the drug along with lactose, cornstarch, and

a binder such as methylcellulose in a planetary mixer. From the brittle fracture index of the formulation, induced by the granulation process. The reductions in the brittle fracture index in Fig. 24. Wet granulation puts this formulation in the

Although this example is not a direct comparison, Bansal and co-workers reported a negative effect on the dissolution rate. They reported that wet granulation with microcrystalline cellulose, which is a common binder, created a hydrated form of the drug. Wet massing with larger amounts of binder created a dissolution profile (Fig. 25) that was more similar to the original formulation. For the reason, this example illustrates the effect of granulation on the performance of the formulation.

Rangaiah and co-workers reported that granulation (slugging) and wet granulation



**Fig. 24** Modification of brittle fracture index: operational versus modified. (From Ref. 123.)



of slugged HPMC and acetaminophen granules: squares, 5 MPa; upward triangles, 10 MPa; diamonds, 100 MPa. (From Ref. 123.)

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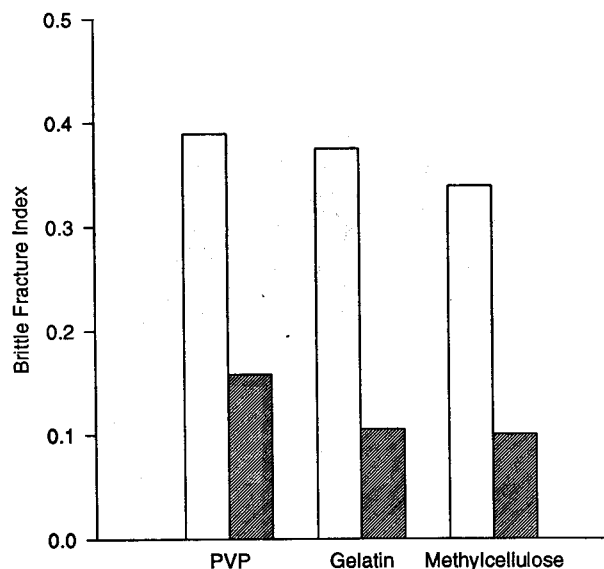
ing options to choose from when an important component of the formulation is characterized in the commercial literature. These examples can be used to illustrate the importance of direct compression in the comparison of various granulation methods (Fig. 24). The first category addresses the question of which method is best for this chapter; namely, which method is best modified or improved with wet

metronidazole was a difficult compound to granulate because it was prone to agglomeration. The characteristics of formulations granulated with lactose, cornstarch, and

a binder such as methylcellulose or gelatin. Wet granulation of this formulation in a planetary mixer was achieved with water as a binder solution. From the brittle fracture index, the authors found the brittle characteristics of the formulation, induced by the drug, were largely eliminated [78,123]. The reductions in the brittle fracture index after wet granulation are shown in Fig. 24. Wet granulation always reduced the BFI to below 0.2, which puts this formulation in the safe region for capping [78,123].

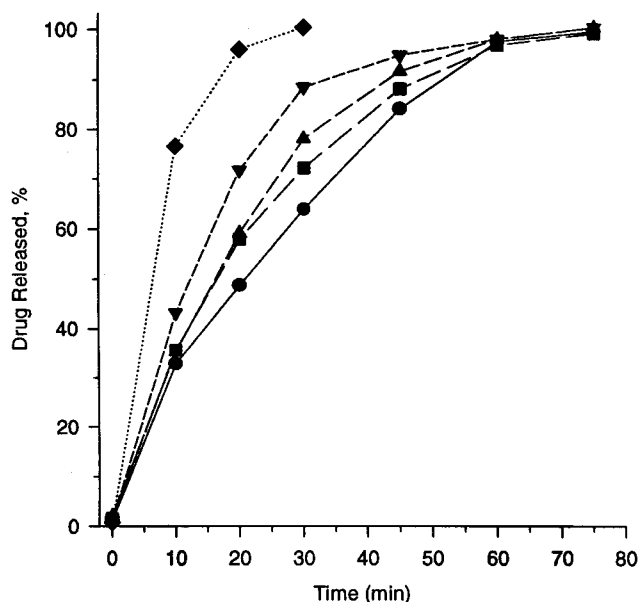
Although this example illustrates a positive aspect of wet granulation, Bansal and co-workers reported that wet granulation could have a significant negative effect on the dissolution profile of a compound [124]. These authors reported that wet granulating a formulation containing naproxen sodium, microcrystalline cellulose, and PVP reduced the dissolution rate of the drug. Wet massing with larger quantities of water also negatively affected the dissolution profile (Fig. 25). The authors hypothesized that wet granulation created a hydrated form of the drug that was less soluble [124]. Whatever the reason, this example illustrates why characterizing the influence of granulation on the performance of the final product is essential.

Rangaiah and co-workers investigated the effect of both dry granulation (slugging) and wet granulation in comparison with direct compression



**Fig. 24** Modification of brittleness of metronidazole formulations as measured by the brittle fracture index: open bars, direct compression; closed bars, wet granulated. (From Ref. 123.)





**Fig. 25** Dissolution profiles of naproxen sodium tablets prepared using different amounts of water: diamonds, dry blending; downward triangles, 110 g water; upward triangles, 125 g water; squares, 150 g water; circles, 175 g water. (From Ref. 124.)

for a formulation of norfloxacin [125]. Both tablet hardness and dissolution were quite dependent on the final granule size of the blend before compaction. The dry granulation exhibited a slower dissolution rate, although the average granule size was higher [125]. This is an important point to remember when attempting to compare processes. Other factors, such as granule size, could affect the properties of concern. An understanding of the influence of these factors will enable the formulation scientist to properly differentiate processes.

Beten and co-workers investigated the effect of dry granulation on the compression characteristics of acetylsalicylic acid-microcrystalline cellulose tablets [126]. When using an instrumented single-station tablet press the dry, granulated formulation exhibited a loss in compressibility. Yield pressures, using Heckel analysis, increased by approximately 500% when compared with a direct compression formulation of identical composition [126]. The loss in plasticity after dry granulation was attributed to the poorer-tableting performance of the formulation.

Examples of characterization as a method for differentiating granulation properties can be instructive to the formulation scientist. Chalmers and

Elworthy compared the effusions of granulated tablets versus dry-granulated tablets of identical compositions, even when significant differences in granule size were present. The granulated blends had a lower moisture sorption, no mercury intrusion, and were comparable in dissolution. These results were reported by Zuretti and co-workers [127]. Massing methods against the final tablets produced by dry granulation showed no difference from wet-massing methods, and the tablets could not be dissolved [127].

An interesting illustration of the effect of granulation on dissolution was offered by Nough and co-workers for fluid bed granulation [129]. Physical properties such as friability, surface area, and bulk density of fluid bed-manufactured granules and conventionally massed granules were very similar. Similar dissolution properties of an experimental granule and fluid bed granulated [130].

#### IV. SUMMARY

The characterization tools that are available to the formulation scientist in the pharmaceutical industry are vast (e.g., X-ray diffraction) to the point that this range of tools and techniques is overwhelming. This range of pharmaceutical granulation characterization tools is not to be an exhaustive treatise but to provide a starting point where the formulation scientist can solve problems in the development of new granulation techniques. As techniques are improved and new techniques from other fields are introduced, the formulation scientist has to choose. This, undoubtedly, is a challenge in developing more robust formulations.

#### ACKNOWLEDGMENT

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Elworthy compared the effects of wet massing oxytetracycline tablet formulations versus dry-granulated (slugged) formulations [127]. With identical compositions, even when the mean granule size was similar, there were significant differences between wet- and dry-granulated blends. Dry-granulated blends had a lower intragranular porosity, as measured with mercury intrusion, and were considerably stronger mechanically [127]. Similar results were reported by Zuurman et al. in the comparison of numerous wet-massing methods against the dry granulation of lactose [128]. However, the final tablets produced by dry granulation were weaker than those produced from wet-massing methods, taking longer to disintegrate as well as to dissolve [127].

An interesting illustration of characterization during process comparison was offered by Nough for conventional, low shear granulation and fluid bed granulation [129]. Physical properties of sulfadiazine granules, such as friability, surface area, and bulk density, were sensitive to process. In general fluid bed-manufactured granules were less friable and less dense than the conventionally massed granules [129]. The final tablet properties, however, were very similar. Similar results were also observed for the final tablet properties of an experimental protein when either conventionally massed or fluid bed granulated [130].

#### IV. SUMMARY

The characterization tools that are currently available to the granulation scientist in the pharmaceutical industry can range from the most sophisticated (e.g., X-ray diffraction) to the most unsophisticated (e.g., a friabilator). Yet, this range of tools and techniques is required throughout the development of pharmaceutical granulations. Although the intention of this chapter was not to be an exhaustive treatment of all characterization methods, it does provide a starting point whereby the formulation scientist could begin to solve problems in the development of granulations. In the future, as techniques are improved and new techniques, particularly those that are imported from other fields, are introduced, the scientist will have a larger arsenal from which to choose. This, undoubtedly, will increase the scientist's effectiveness in developing more robust formulations for commercial manufacturing.

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## REFERENCES

1. HG Brittain, SJ Bogdanowich, DE Bugay, J DeVincentis, G Lewen, AW Newman. Physical characterization of pharmaceutical solids. *Pharm Res* 8: 963, 1991.
2. R Rupp. Flow and other properties of granulates. *Boll Chim Farm* 116:251, 1977.
3. K Ridgway, R Rupp. *J Pharm Pharmacol* 21:30S, 1969.
4. FA Shergold. The effect of sieve loading on the results of sieve analysis of natural sands. *J Soc Chem Ind* 65:245, 1946.
5. DE Fonner, GS Banker, J Swarbrick. Micromeritics of granular pharmaceutical solids II: Factors involved in the sieving of pharmaceutical granules. *J Pharm Sci* 55:576, 1966.
6. PTA Stevens. The relationship between particle size distribution of granules and weight variation of tablets. *Acta Pharm Technol* 26:304, 1980.
7. S Byrn, R Pfeiffer, M Ganey, C Hoiberg, G Poochikian. Pharmaceutical solids: a strategic approach to regulatory considerations. *Pharm Res* 12:945, 1995.
8. KR Morris, AW Newman, DE Bugay, SA Randive, AK Singh, M Szyper, SA Varia, HG Brittain, ATM Serajuddin. Characterization of humidity-dependent changes in crystal properties of a new HMB-CoA reductase inhibitor in support of its dosage form development. *Int J Pharm* 108:195, 1994.
9. JT Carstensen. *Pharmaceutical Principles of Solid Dosage Forms*. Lancaster, PA: Technomic Publishing, 1993.
10. L Hellén, J Yliruusi, P Merkkü, E Kristofferson. Process variables of instant granulator and spheroniser: I. Physical properties of granules, extrudate and pellets. *Int J Pharm* 96:197, 1993.
11. DM Lipps, AM Sakr. Characterization of wet granulation process parameters using response surface methodology. I. Top-spray fluidization. *J Pharm Sci* 83:937, 1994.
12. T Schaefer, O Wörts. Control of fluidized bed granulation. III. Effects of inlet air distribution. Control of moisture content of granules in the drying phase. *Arch Pharm Chem Sci Ed* 6:1, 1978.
13. MWY Wong, AG Mitchell. Physicochemical characterization of a phase change produced during the wet granulation of chlorpromazine hydrochloride and its effects on tableting. *Int J Pharm* 88:261, 1992.
14. G Gold, BT Palermo. Hopper flow electrostatics of tableting material I. Instrumentation and acetaminophen formulations. *J Pharm Sci* 54:310, 1965.
15. AA Chalmers, PH Elworthy. Oxytetracycline tablet formulations: effect of variations in binder concentration and volume on granule and tablet properties. *J Pharm Pharmacol* 28:228, 1976.
16. CF Harwood, N Pilpel. Granulation of griseofulvin. *J Pharm Sci* 57:478, 1968.
17. PC Carmen. The determination of the specific surface of powders. I. *J Soc Chem Ind* 57:225, 1938.
18. S Brunauer, PH Emmett, E Teller. Adsorption of gases in multimolecular layers. *J Am Chem Soc* 60:309, 1938.
19. PJ Rigden. The specific surface area of powders determined by the air-permeability method. *J Pharm Sci* 74:100, 1985.
20. G Alderborn, M Duberg, C X. Measurement of tablet porosity. *J Pharm Sci* 74:100, 1985.
21. JM Hayes, P Rossi-Doria. Characterization. Bristol: J Pharm Sci, 1985.
21. WA Strickland, LW Busse. Determination of porosity. *J Pharm Sci* 45:482, 1956.
23. D Ganderton, BM Hunter. Granulation and by massing and by massing. *J Pharm Sci* 74:100, 1985.
24. H Rumpf. The strength of agglomerates. *Agglomeration*. New York: Wiley, 1962.
25. K Ridgway, E Shotton, J. *J Pharm Sci* 54:310, 1965.
26. G Gold, RN Duvall, BT Palermo. Granulation factor I: instrument. *J Pharm Sci* 54:310, 1965.
27. A Mehta, MA Zoglio, JT Carstensen. The strength of granules. *J Pharm Sci* 54:310, 1965.
28. PM Hill. Starch paste granules. *J Pharm Sci* 65:310, 1976.
29. AM Marks, JJ Sciarra. Efficiency and their corresponding tablet. *J Pharm Sci* 65:310, 1976.
30. M Wikberg, G Alderborn. Tablets. IV. The effect of granulation on the compactibility of some tablets. *J Pharm Sci* 65:310, 1976.
31. L Lachman, HA Lieberman. *Pharmaceutical Technology*. Philadelphia: Lea & Febiger, 1973.
32. RL Carr. Evaluating the flow of powders. *J Pharm Sci* 69:100, 1980.
33. RE Gordon, TW Rosansk. Granulation technology and tablet. *J Pharm Sci* 69:100, 1980.
34. KD Ertel, MA Zoglio, W. Granulation IV—effect of granulation on the compactibility of some tablets. *Drug Dev Ind Pharm* 10:127T, 1958.
35. N Pilpel. The flow of powders. *J Pharm Sci* 54:310, 1965.
36. FQ Danish, EL Parrott. *J Pharm Sci* 60:548, 1971.
37. P York. Powder failure tests. *J Pharm Sci* 69:100, 1980.
38. D. Train. Some aspects of granulation. *Pharmacol* 10:127T, 1958.
39. G Gold, RN Duvall, BT Palermo. Granulation factor I: instrument. *J Pharm Sci* 54:310, 1965.

- ay, J DeVincentis, G Lewen, AW  
armaceutical solids. *Pharm Res* 8:  
anulates. *Boll Chim Farm* 116:251,  
21:30S, 1969.  
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046.  
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considerations. *Pharm Res* 12:945,  
Randive, AK Singh, M Szyper, SA  
acterization of humidity-dependent  
B-CoA reductase inhibitor in sup-  
*J Pharm* 108:195, 1994.  
of Solid Dosage Forms. Lancaster,  
erson. Process variables of instant  
operties of granules, extrudate and  
wet granulation process parameters  
op-spray fluidization. *J Pharm Sci*  
bed granulation. III. Effects of inlet  
nt of granules in the drying phase.  
mical characterization of a phase  
on of chlorpromazine hydrochloride  
8:261, 1992.  
ostatics of tableting material I. In-  
tions. *J Pharm Sci* 54:310, 1965.  
eline tablet formulations: effect of  
ume on granule and tablet proper-  
eofulvin. *J Pharm Sci* 57:478, 1968.  
ecific surface of powders. I. *J Soc*  
rption of gases in multimolecular
19. PJ Rigden. The specific surface of powders. A modification of the theory of the air-permeability method. *J Soc Chem Ind* 66:130, 1947.
  20. G Alderborn, M Duberg, C Nystrom. Studies on direct compression of tablets X. Measurement of tablet surface area by permeametry. *Powder Technol* 41:49, 1985.
  21. JM Hayes, P Rossi-Doria. Principles and Applications of Pore Structural Characterization. Bristol: JW Arrowsmith, 1985.
  21. WA Strickland, LW Busse, T Higuchi. The physics of tablet compression XI. Determination of porosity of tablet granulations. *J Am Pharm Assoc Sci Ed* 45:482, 1956.
  23. D Ganderton, BM Hunter. A comparison of granules prepared by pan granulation and by massing and screening. *J Pharm Pharmacol* 23:1S, 1971.
  24. H Rumpf. The strength of granules and agglomerates. In: WA Knepper, ed. Agglomeration. New York: Wiley Interscience, 1962, p. 379.
  25. K Ridgway, E Shotton, J Glasby. *J Pharm Pharmacol* 21:195, 1969.
  26. G Gold, RN Duvall, BT Palermo, RL Hurtle. Granule strength as a formulation factor I: instrumentation. *J Pharm Sci* 60:922, 1971.
  27. A Mehta, MA Zoglio, JT Carstensen. Ball milling as a measure of crushing strength of granules. *J Pharm Sci* 67:905, 1978.
  28. PM Hill. Starch paste granulations: binder dilution effects on granulations and tablets. *J Pharm Sci* 65:313, 1976.
  29. AM Marks, JJ Sciarra. Effect of size on other physical properties of granules and their corresponding tablets. *J Pharm Sci* 57:497, 1968.
  30. M Wikberg, G Alderborn. Compression characteristics of granulated materials. IV. The effect of granule porosity on the fragmentation propensity and the compactibility of some granulations. *Int J Pharm* 69:239, 1991.
  31. L Lachman, HA Lieberman, JL Kanig. Theory and Practice of Industrial Pharmacy. Philadelphia: Lea & Febiger, 1986.
  32. RL Carr. Evaluating the flow properties of solids. *Chem Eng* 72:163, 1965.
  33. RE Gordon, TW Rosanske, DE Fonner, NR Anderson, GS Banker. Granulation technology and tablet characterization. In: HA Lieberman, L Lachman, JB Schwartz, eds. *Pharmaceutical Dosage Forms: Tablets*. New York: Marcel Dekker, 1990.
  34. KD Ertel, MA Zoglio, WA Ritschel, JT Carstensen. Physical aspects of wet granulation IV—effect of kneading time on dissolution rate and tablet properties. *Drug Dev Ind Pharm* 16:963, 1990.
  35. N Pilpel. The flow of powders and granular solids. *Br Chem Eng* 11:699, 1966.
  36. FQ Danish, EL Parrott. Flow rates of solid particulate pharmaceuticals. *J Pharm Sci* 60:548, 1971.
  37. P York. Powder failure testing—pharmaceutical applications. *Int J Pharm* 6:89, 1980.
  38. D. Train. Some aspects of the property of angle of repose of powders. *J Pharm Pharmacol* 10:127T, 1958.
  39. G Gold, RN Duvall, BT Palermo, JG Slater. Powder flow studies II: effect of glidants on flow rate and angle of repose. *J Pharm Sci* 55:1291, 1966.

40. AW Jenike. Gravity Flow of Solids, Bulletin 108. Salt Lake City: Utah Engineering Experimental Station, University of Utah, 1961.
41. EN Hiestand. The determination of some important physical properties of powders. *Pharm Ind* 34:262, 1972.
42. JF Carr, DM Walker. An annular shear cell for granular materials. *Powder Technol* 1:369, 1968/1969.
43. GE Amidon, ME Houghton. Powder flow testing in preformulation and formulation development. *Pharm Manuf*, 1985.
44. CM Sinko, GT Carlson, BA Beckwith. Mechanical property modification of powder. Proceedings of the First International Particle Technology Forum, Denver CO, 1994, p. 121.
45. BC Hancock, P York, RC Rowe, MD Parker. Characterization of wet masses using a mixer torque rheometer: 1. Effect of instrument geometry. *Int J Pharm* 76:239, 1991.
46. RC Rowe, MD Parker. Mixer torque rheometry: an update. *Pharm Technol* 20:74, 1994.
47. M Ritala, S Virtanen. The effect of binder solution quantity and lactose particle size on granule properties. *Acta Pharm Nord* 3:229, 1991.
48. HG Kristensen, T Schaefer. Granulation: a review on pharmaceutical wet-granulation. *Drug Dev Ind Pharm* 13:803, 1987.
49. DJ Holve, TL Harvill. In-process particle size distribution measurements. *Ceram Ind XX*:19, 1995.
50. I Krycer, DG Pope, JA Hersey. The interpretation of powder compaction data—a critical review. *Drug Dev Ind Pharm* 8:307, 1982.
51. MJ Juslin, MJ Jaervinen. *Farm Notisbl* 79:1, 1970.
52. K Ridgway, PH Rosser. *J Pharm Pharmacol* 23:202S, 1971.
53. CJ de Blaey, J Polderman. *Pharm Weekblad* 105:241, 1970.
54. S Gillard, P Touré, M Roland. *Pharm Acta Helv* 51:226, 1976.
55. CJ de Blaey, AB Weekers-Andersen, J Polderman. *Pharm Weekblad* 106:893, 1971.
56. RJ Oates, AG Mitchell. Calculation of punch displacement and work of powder compaction on a rotary tablet press. *J Pharm Pharmacol* 41:517, 1989.
57. JE Rees, PJ Rue, SC Richardson. Work-of-failure measurements on formulated tablets. *J Pharm Pharmacol* 29:38P, 1977.
58. P York. *J Pharm Pharmacol* 31:244, 1979.
59. RJ Roberts, RC Rowe. The effect of the relationship between punch velocity and particle size on the compaction behaviour of materials with varying deformation mechanisms. *J Pharm Pharmacol* 38:567, 1986.
60. RJ Roberts, RC Rowe. The effect of punch velocity on the compaction of a variety of materials. *J Pharm Pharmacol* 37:377, 1985.
61. DW Danielson, WT Morehead, EG Rippie. Unloading and postcompression viscoelastic stress versus strain behavior of pharmaceutical solids. *J Pharm Sci* 72:342, 1983.
62. WT Morehead, EG Rippie. Timing relationships among maxima of punch and die-wall stress and punch displacement during compaction of viscoelastic solids. *J Pharm Sci* 79:1020, 1990.
63. SK Dwivedi, RJ Oates. The effect of punch velocity on the stress relaxation during compaction. *J Pharm Sci* 43:673, 1991.
64. LE Holman. The compaction of powders based on percolation theory. *J Pharm Sci* 64:233, 1991.
65. LE Holman, H Leuenberger. The relationship between the compaction of powders and the percolation theory. *Technol* 64:233, 1991.
66. LE Holman. The compaction of powders: an illustration of percolation theory. *J Pharm Sci* 64:233, 1991.
67. LE Holman, H Leuenberger. The mechanical properties of powders. *J Pharm Sci* 46:35, 1988.
68. C Nystrom, W Alex, J Oates. The measurement of tablets. *Acta Pharm Nord* 3:229, 1991.
69. H Leuenberger, R Leuenberger. The compaction phenomenon. *J Pharm Sci* 64:233, 1991.
70. EN Hiestand, CB Peacock. The relationship between the compaction of powders and the percolation theory. *Technol* 64:233, 1991.
71. EN Hiestand. Tablet compaction. *J Pharm Sci* 64:233, 1991.
72. RJ Roberts, RC Rowe. The compaction of materials—a pragmatic approach. *J Pharm Sci* 64:233, 1991.
73. F Bassam, P York, RC Rowe. The compaction of materials as pharmaceutical excipients. *J Pharm Sci* 64:233, 1991.
74. EN Hiestand, JM Bane. The compaction of powders. *J Pharm Sci* 64:233, 1991.
75. EN Hiestand. Dispersions. *Pharm Sci* 74:768, 1991.
76. AB Mashadi, JM Newkome. The compaction of materials ( $K_{ic}$ ) of compacted powders. *Pharm Pharmacol* 40:517, 1989.
77. GW Radebaugh, SR Rippie. The properties of compacted powders. *Int J Pharm* 38:145, 1984.
78. EN Hiestand, DP Smith. The compaction of materials. *Pharm Sci* 74:768, 1991.
79. OA Itiola, N Pilpel. The compaction of materials. *J Pharm Sci* 72:342, 1983.
80. H Gucluyildiz, GS Barakat. The distribution of aspirin. *J Pharm Sci* 72:342, 1983.
81. M Wikberg, G Alderberg. The effect of some lactose granules. *J Pharm Sci* 72:342, 1983.

tin 108. Salt Lake City: Utah En-  
 of Utah, 1961.  
 e important physical properties of  
 ell for granular materials. Powder  
 testing in preformulation and for-  
 5.  
 mechanical property modification of  
 ional Particle Technology Forum,  
 er. Characterization of wet masses  
 f instrument geometry. Int J Pharm  
 omety: an update. Pharm Technol  
 solution quantity and lactose par-  
 m Nord 3:229, 1991.  
 a review on pharmaceutical wet-  
 1987.  
 ize distribution measurements. Ce-  
 rpretation of powder compaction  
 arm 8:307, 1982.  
 1, 1970.  
 ol 23:202S, 1971.  
 ad 105:241, 1970.  
 a Helv 51:226, 1976.  
 derman. Pharm Weekblad 106:893,  
 ch displacement and work of pow-  
 Pharm Pharmacol 41:517, 1989.  
 f-failure measurements on formu-  
 1977.  
 elationship between punch velocity  
 iour of materials with varying de-  
 l 38:567, 1986.  
 h velocity on the compaction of a  
 7:377, 1985.  
 e. Unloading and postcompression  
 of pharmaceutical solids. J Pharm  
 ships among maxima of punch and  
 ing compaction of viscoelastic sol-

63. SK Dwivedi, RJ Oates, AG Mitchell. Peak offset times as an indication of stress relaxation during tableting on a rotary tablet press. *J Pharm Pharmacol* 43:673, 1991.
64. LE Holman. The compaction behavior of particulate materials. An elucidation based on percolation theory. *Powder Technol* 66:265, 1991.
65. LE Holman, H Leuenberger. The significance of slopes of the semilogarithmic relationship between hardness and solid fraction of porous compacts. *Powder Technol* 64:233, 1991.
66. LE Holman. The compressibility of pharmaceutical particulate systems. An illustration of percolation. *Int J Pharm* 71:81, 1991.
67. LE Holman, H Leuenberger. The relationship between solid fraction and mechanical properties of compacts—the percolation theory model approach. *Int J Pharm* 46:35, 1988.
68. C Nystrom, W Alex, K Malmqvist. A new approach to tensile strength measurement of tablets. *Acta Pharm Suec* 14:317, 1977.
69. H Leuenberger, R Leu. The formation of a tablet: a site-bond percolation phenomenon. *J Pharm Sci* 81:976, 1992.
70. EN Hiestand, CB Peot. Tensile strength of compressed powders and an example of incompatibility as end-point on shear yield locus. *J Pharm Sci* 63:605, 1974.
71. EN Hiestand. Tablet bond I. A theoretical model. *Int J Pharm* 67:217, 1991.
72. RJ Roberts, RC Rowe. The compaction of pharmaceutical and other model materials—a pragmatic approach. *Chem Eng Sci* 42:903, 1987.
73. F Bassam, P York, RC Rowe, RJ Roberts. Young's modulus of powders used as pharmaceutical excipients. *Int J Pharm* 64:55, 1990.
74. EN Hiestand, JM Bane, EP Strzelinski. Impact test for hardness of compressed powder compacts. *J Pharm Sci* 60:758, 1971.
75. EN Hiestand. Dispersion forces and plastic deformation in tablet bond. *J Pharm Sci* 74:768, 1985.
76. AB Mashadi, JM Newton. Determination of the critical stress intensity factor ( $K_{IC}$ ) of compacted pharmaceutical powders by the double torsion method. *J Pharm Pharmacol* 40:597, 1988.
77. GW Radebaugh, SR Babu, JN Bondi. Characterization of the viscoelastic properties of compacted pharmaceutical powders by a novel nondestructive technique. *Int J Pharm* 57:95, 1989.
78. EN Hiestand, DP Smith. Indices of tableting performance. *Powder Technol* 38:145, 1984.
79. OA Itiola, N Pilpel. Formulation effects on the mechanical properties of metronidazole tablets. *J Pharm Pharmacol* 43:145, 1991.
80. H Gucluyildiz, GS Banker, GE Peck. Determination of porosity and pore-size distribution of aspirin tablets relevant to drug stability. *J Pharm Sci* 66:407, 1977.
81. M Wikberg, G Alderborn. Compression characteristics of granulated materials. VII. The effect of intragranular binder distribution on the compactibility of some lactose granulations. *Pharm Res* 10:88, 1993.

82. AB Selkirk, D Ganderton. An investigation of the pore structure of tablets of sucrose and lactose by mercury porosimetry. *J Pharm Pharmacol* 22:79S, 1970.
83. JS Hardman, BA Lilley. *Proc R Soc Lond A* 333:183, 1973.
84. AH de Boer, GK Bolhuis, CF Lerk. *Powder Technol* 25:75, 1978.
85. M Duberg, C Nystrom. *Acta Pharm Suec* 19:147, 1982.
86. M Wikberg, G Alderborn. Compression characteristics of granulated materials: VI. Pore size distributions, assessed by mercury penetration of compacts of two lactose granulations with different fragmentation properties. *Int J Pharm* 84:191, 1992.
87. H Nogami, H Fukuzawa, Y Nakai. Studies on tablet disintegration. I. The effect of penetrating rate on tablet disintegration. *Chem Pharm Bull* 11:1389, 1963.
88. MH Rubenstein, JI Wells. Generated surface area measurement of disintegrating tablets. *J Pharm Pharmacol* 29:363, 1977.
89. AJ Forlano, L Chavkin. The effect of granule size upon disintegration time and capping in compressed tablets. *J Am Pharm Assoc Sci Ed* 49:67, 1960.
90. JA Hersey. Methods available for the determination of an in vitro dissolution rate. *Manuf Chem Aerosol News* 40:32, 1969.
91. RJ Hintz, KC Johnson. The effect of particle size distribution on dissolution rate and oral absorption. *Int J Pharm* 51:9, 1989.
92. C-H Liu, S-C Chen, Y-H Kao, C-C Kao, TD Sokoloski, M-T Sheu. Properties of hydroxypropylmethylcellulose granules produced by water spraying. *Int J Pharm* 100:241, 1993.
93. AJ Romero, G Lukas, CT Rhodes. Influence of different sources on the processing and biopharmaceutical properties of high-dose ibuprofen formulations. *Pharm Acta Helv* 66:34, 1991.
94. T Cutt, JT Fell, PJ Rue, MS Spring. Granulation and compaction of a model system. I. Granule properties. *Int J Pharm* 33:81, 1986.
95. NA Armstrong, FSS Morton. The effect of granulating agents on the elasticity and plasticity of powders. *J Powder Bulk Sol Technol* 20:32.
96. M Wikberg, G Alderborn. Compression characteristics of granulated materials. II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements. *Int J Pharm* 62:229, 1990.
97. AA Chalmers, PH Elworthy. Oxytetracycline tablet formulations: the effect of wet mixing time, particle size and batch variation on granule and tablet properties. *J Pharm Pharmacol* 82:239, 1976.
98. J Akbuga. Studies on granulation properties of furosemide: effects of process and product variables on size and properties of granules. *Pharmazie* 45:50, 1990.
99. BM Hunter, D Ganderton. The influence on pharmaceutical granulation of the type and capacity of mixers. *J Pharm Pharmacol* 25:71P, 1973.
100. WO Opankunle, BR Bhutani, VN Bhatia. Drying rates of tablet granulations II: effect of particle size and granular densities. *J Pharm Sci* 64:1023, 1975.
101. RJ Timko, JS Barrett, PA McHugh, ST Chen, HA Rosenberg. Use of a motor load analyzer to monitor the granulation process in a high density mixer. *Drug Dev Ind Pharm* 13:405, 1987.
102. P Holm, T Schaefer, H... IV. Effects of process... *Powder Technol* 43:22...
103. T Schaefer, P Holm, H... high shear mixer. *Pharm...*
104. D Vojnovic, P Selenati... scale high shear mixer. *Pharm...*
105. D Vojnovic, M Moneg... zation of several respo... *Pharm* 19:1479, 1993.
106. P Holm, O Jungersen, ... mixers. Part I: effects... 806, 1983.
107. P Wehrli, P Nobelis, A... interesting statistical to... wet granulation in a hi... *Pharm* 92:143, 1993.
108. T Schaefer, HH Bak, A... Kristensen. Granulation... of process variables an... *Pharm* 17:1437, 1991.
109. GJB Horsthuis, JAH va... on the upscaling param... *Pharm* 17:1437, 1991.
110. M Banks, ME Aulton. *J Pharm* 17:1437, 1991.
111. BV Andreev, VI Gorod... pharmaceutical powder... *Pharm* 17:1437, 1991.
112. MH Alkan, A Yuksel... amount on the final gra... *Pharm* 17:1437, 1991.
113. Z Ormós, K Pataki, B... The effects of the amou... formed in a fluidized b... *Pharm* 17:1437, 1991.
114. Z Ormós, K Pataki, B... Calculation of the feed... 1973.
115. WL Davies, WT Gloor... a fluidized bed I: Effe... granulation. *J Pharm Sc...*
116. WL Davies, WT Gloor... a fluidized bed II: effec... ulations and compress... *J Pharm Sc...*
117. F Higashide, Y Miki, Y... uniformity on particle s... 1985.
118. M Meshali, HM El-Bar... to evaluate granulation... 1983.

on of the pore structure of tablets of  
metry. *J Pharm Pharmacol* 22:79S,  
d A 333:183, 1973.  
der Technol 25:75, 1978.  
19:147, 1982.  
characteristics of granulated materi-  
by mercury penetration of compacts  
ent fragmentation properties. *Int J*  
ies on tablet disintegration. I. The  
gration. *Chem Pharm Bull* 11:1389,  
urface area measurement of disinte-  
3, 1977.  
anule size upon disintegration time  
*Pharm Assoc Sci Ed* 49:67, 1960.  
termination of an in vitro dissolution  
1969.  
icle size distribution on dissolution  
9, 1989.  
D Sokoloski, M-T Sheu. Properties  
s produced by water spraying. *Int J*  
nce of different sources on the pro-  
s of high-dose ibuprofen formula-  
ulation and compaction of a model  
33:81, 1986.  
f granulating agents on the elasticity  
*Sol Technol* 20:32.  
characteristics of granulated materi-  
n during compression by tablet per-  
*J Pharm* 62:229, 1990.  
eline tablet formulations: the effect  
atch variation on granule and tablet  
76.  
of furosemide: effects of process and  
granules. *Pharmazie* 45:50, 1990.  
on pharmaceutical granulation of  
*Pharmacol* 25:71P, 1973.  
Drying rates of tablet granulations  
sities. *J Pharm Sci* 64:1023, 1975.  
en, HA Rosenberg. Use of a motor  
process in a high density mixer. *Drug*

102. P Holm, T Schaefer, HG Kristensen. Granulation in high-speed mixers. Part IV. Effects of process conditions on power consumption and granule growth. *Powder Technol* 43:225, 1985.
103. T Schaefer, P Holm, HG Kristensen. Wet granulation in a laboratory scale high shear mixer. *Pharm Ind* 52:1147, 1990.
104. D Vojnovic, P Selenati, F Rubessa, M Moneghini. Wet granulation in a small scale high shear mixer. *Drug Dev Ind Pharm* 18:961, 1992.
105. D Vojnovic, M Moneghini, F Rubessa, A Zanchetta. Simultaneous optimization of several response variables in a granulation process. *Drug Dev Ind Pharm* 19:1479, 1993.
106. P Holm, O Jungersen, T Schaefer, HG Kristensen. Granulation in high speed mixers. Part I: effects of process variables during kneading. *Pharm Ind* 45:806, 1983.
107. P Wehrle, P Nobelis, A Cuiné, A Stamm. Response surface methodology: an interesting statistical tool for process optimization and validation: example of wet granulation in a high-shear mixer. *Drug Dev Ind Pharm* 19:1637, 1993.
108. T Schaefer, HH Bak, A Jaegerskou, A Kristensen, JR Svensson, P Holm, HG Kristensen. Granulation in different types of high speed mixers. Part I: effects of process variables and up-scaling. *Pharm Ind* 48:1083, 1986.
109. GJB Horsthuis, JAH van Laarhoven, RCBM van Rooij, H Vromans. Studies on the upscaling parameters of the Gral high shear granulation process. *Int J Pharm* 92:143, 1993.
110. M Banks, ME Aulton. Fluidised-bed granulation: a chronology. *Drug Dev Ind Pharm* 17:1437, 1991.
111. BV Andreev, VI Gorodnichev, SA Minina, HM El-Banna. Granule growth of pharmaceutical powders in a fluidized bed. *Pharm Ind* 42:1304, 1980.
112. MH Alkan, A Yuksel. Granulation in a fluidized bed II. Effect of binder amount on the final granule. *Drug Dev Ind Pharm* 12:1529, 1986.
113. Z Ormós, K Pataki, B Csukás. Studies on granulation in a fluidized bed II. The effects of the amount of the binder on the physical properties of granules formed in a fluidized bed. *Hung J Ind Chem* 1:307, 1973.
114. Z Ormós, K Pataki, B Csukás. Studies on granulation in a fluidized bed III. Calculation of the feed rate of granulating liquid. *Hung J Ind Chem* 1:463, 1973.
115. WL Davies, WT Gloor. Batch production of pharmaceutical granulations in a fluidized bed I: Effects of process variables on physical properties of final granulation. *J Pharm Sci* 60:1869, 1971.
116. WL Davies, WT Gloor. Batch production of pharmaceutical granulations in a fluidized bed II: effects of various binders and their concentrations on granulations and compressed tablets. *J Pharm Sci* 61:618, 1972.
117. F Higashide, Y Miki, Y Nozawa, K Ishibashi. Dependence of drug content uniformity on particle sizes in fluidized bed granulation. *Pharm Ind* 47:1202, 1985.
118. M Meshali, HM El-Banna, H El-Sabbagh. Use of fractional factorial design to evaluate granulations prepared in a fluidized bed. *Pharmazie* 38:323, 1983.



119. S Malkowska, KA Khan. Effect of re-compression on the properties of tablets prepared by dry granulation. *Drug Dev Ind Pharm* 9:331, 1983.
120. P Hervieu, F Dehont, E Jerome, A Delacourte, JC Guyot. Granulation of pharmaceutical powders by compaction. An experimental study. *Drug Dev Ind Pharm* 20:65, 1994.
121. F Jaminet, H Hess. Studies on compaction and dry granulation. *Pharm Acta Helv* 41:39, 1966.
122. Y Kawashima, H Takeuchi, T Hino, T Niwa, T-L Lin, F Sekigawa. Preparation of a sustained-release matrix tablet of acetaminophen with pulverized low-substituted hydroxypropylcellulose via dry granulation. *Chem Pharm Bull* 41:1827, 1993.
123. OA Itiola, N Pilpel. Tableting characteristics of metronidazole formulations. *Int J Pharm* 31:99, 1986.
124. P Bansal, K Haribhakti, V Subramanian, F Plakogiannis. Effect of formulation and process variables on the dissolution profile of naproxen sodium from tablets. *Drug Dev Ind Pharm* 20:2151, 1994.
125. KV Rangaiah, SC Chattaraj, SK Das. Effects of process variables and excipients on tableting parameters of norfloxacin tablets. *Drug Dev Ind Pharm* 20:2175, 1994.
126. DB Beten, N Yüksel, T Baykara. The changes in the mechanic properties of a direct tableting agent microcrystalline cellulose by precompression. *Drug Dev Ind Pharm* 20:2333, 1994.
127. AA Chalmers, PH Elworthy. Oxytetracycline tablet formulations: the influence of excipients and the method of granulation. *J Pharm Pharmacol* 28:234, 1976.
128. K Zuurman, KA Riepma, GK Bolhuis, H Vromans, CF Lerk. The relationship between bulk density and compactibility of lactose granulations. *Int J Pharm* 102:1, 1994.
129. ATI Nouh. The effect of variations in concentration and type of binder on the physical characteristics of sulfadiazine tablets and granulations prepared by wet and fluidised-bed granulation method. *Pharm Ind* 48:670, 1986.
130. MJ Gamlen, H Seager, JK Warrack. The structure and tablet properties of paracetamol granules prepared in a fluidized bed and by wet massing. *Int J Pharm Technol Prod Manuf* 3:108, 1982.

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## Bioavailability Properties

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### I. INTRODUCTION

The most important property of an active ingredient to the "site of action" is its desired pharmacological response, which is variously referred to as its potency or bioavailability.

*Bioavailability* may be defined as the extent of absorption of a drug from

pression on the properties of tablets  
and Pharm 9:331, 1983.

lacourte, JC Guyot. Granulation of  
An experimental study. Drug Dev

on and dry granulation. Pharm Acta

Niwa, T-L Lin, F Sekigawa. Prepa-  
t of acetaminophen with pulverized  
a dry granulation. Chem Pharm Bull

stics of metronidazole formulations.

F Plakogiannis. Effect of formulation  
a profile of naproxen sodium from  
994.

ects of process variables and excip-  
in tablets. Drug Dev Ind Pharm 20:

anges in the mechanic properties of  
cellulose by precompression. Drug

cline tablet formulations: the influ-  
ulation. J Pharm Pharmacol 28:234,

Vromans, CF Lerk. The relationship  
of lactose granulations. Int J Pharm

concentration and type of binder on  
e tablets and granulations prepared  
hod. Pharm Ind 48:670, 1986.

e structure and tablet properties of  
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## Bioavailability and Granule Properties

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### I. INTRODUCTION

The most important property of a dosage form is its ability to deliver the active ingredient to the "site of action" in an amount sufficient to elicit the desired pharmacological response. This property of a dosage form has been variously referred to as its physiological availability, biological availability, or bioavailability.

*Bioavailability* may be defined more accurately as the rate and extent of absorption of a drug from its dosage form into the systemic circulation.

Accordingly, the absorption of a drug following intravenous administration is extremely rapid and complete. However, owing to convenience and stability problems, drugs are often administered orally as a tablet or capsule dosage form. Therefore, it is imperative that their rate and extent of absorption in an individual be known accurately. Furthermore, equally important is that the factors that influence the rate and extent of absorption of drugs are also known and understood by formulators.

The subject of bioavailability began to receive growing attention as studies showed that the therapeutic effectiveness of a drug from the dosage form largely depends on the physiological availability of its active ingredient(s), and is a function of the drug concentration in the patient's blood or plasma. The importance of bioavailability in drug therapy, therefore, is that the rate and extent of absorption of a drug from a dosage form can, in fact, affect the patient's response to a drug. In this light, the determination of bioavailability has become one of the ways to assess the *in vivo* performance of a dosage form following its formulation development. However, it must be remembered that bioavailability studies are frequently conducted in normal, fasted, and small numbers of subjects; therefore, the results of these studies may not always reflect the true efficacy relation in patients under treatment conditions.

For many years it was assumed that if a dosage form contained the labeled amount of a drug, its performance could be taken for granted. However, it has been evident for some time now that many factors acting individually or in concert may produce the therapeutic failure.

## II. BIOAVAILABILITY PARAMETERS

In assessing the bioavailability of a drug from a particular dosage form, three parameters are measured following its administration and obtaining the blood drug concentration–time profile (Fig. 1).

1. Peak concentration,  $(C_p)_{\max}$
2. Peak time,  $t_{\max}$
3. The area under the concentration–time curve,  $(AUC)_0^\infty$

The parameters peak time  $t_{\max}$  and peak concentration  $(C_p)_{\max}$  are the measure of the rate of absorption and the area under the concentration–time curve  $(AUC)_0^\infty$  is a measure of the extent of absorption.

### A. Peak Time

The  $t_{\max}$  represents the length of time required to attain the maximum concentration of drug in the systemic circulation. The parameter describes the

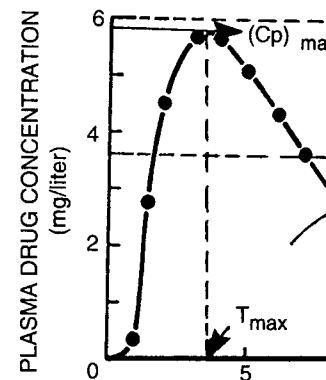


Fig. 1 A graphic representation of the administration of a drug.

onset of the peak level of the drug.  $t_{\max}$  is a measure of the rate of absorption. The smaller is the  $t_{\max}$  value and the earlier the peak time is determined by

$$t_{\max} = \frac{\ln(K_a/K)}{(K_a - K)}$$

where,  $K_a$  and  $K$  are the first-order rate constants, respectively.

Equation (1) clearly indicates that the smaller the rate constant  $K_a$ , the smaller the  $t_{\max}$  value. The onset of action is likely to be determined by

The elimination rate constant  $K$  varies among individuals, and it changes with the route of elimination of the drug (i.e., kidney and liver). The rate constant  $K_a$ , on the other hand, is determined by the dosage form, and the formulation factors. The  $t_{\max}$  is generally reflected in the higher the  $K_a$  value, the smaller the  $t_{\max}$  value. Therefore, by changing the formulation, the  $t_{\max}$  can alter the peak time and the onset of action.

owing intravenous administration, owing to convenience and standardization, are preferred orally as a tablet or capsule. However, the rate and extent of absorption are important factors. Furthermore, equally important factors are the rate and extent of absorption of drugs.

It is to receive growing attention as the bioavailability of a drug from the dosage form is a measure of the availability of its active ingredient in the patient's blood or plasma. In drug therapy, therefore, is that the drug from a dosage form can, in fact, be used. In this light, the determination of the rate and extent of absorption is to assess the in vivo performance of a dosage form. However, it must be noted that these tests are frequently conducted in normal subjects; therefore, the results of these tests may not reflect the efficacy relation in patients under

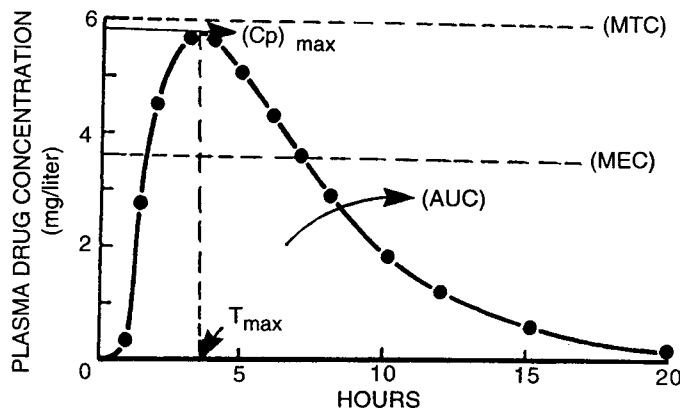
if a dosage form contained the drug could be taken for granted. However, it is now known that many factors acting independently can lead to therapeutic failure.

from a particular dosage form, the rate of absorption and obtaining the rate of absorption (Fig. 1).

concentration-time curve,  $(AUC)_0^\infty$

concentration  $(C_p)_{max}$  are the measure of the rate of absorption. The area under the concentration-time curve is the measure of the extent of absorption.

required to attain the maximum concentration. The parameter describes the



**Fig. 1** A graphic representation of plasma-serum drug concentration data following the administration of a drug by the extravascular route.

onset of the peak level of the biological response; hence, it can be used as a measure of the rate of absorption. The faster the rate of absorption, the smaller is the  $t_{max}$  value and the quicker is the drug's onset of action. The peak time is determined by using Eq. (1).

$$t_{max} = \frac{\ln(K_a/K)}{(K_a - K)} \quad (1)$$

where,  $K_a$  and  $K$  are the first-order absorption and elimination rate constants, respectively.

Equation (1) clearly indicates that the larger the value of the absorption rate constant  $K_a$ , the smaller the value of peak time  $t_{max}$ , and the quicker the onset of action is likely to be.

The elimination rate constant  $K$  is constant for a drug in normal healthy individuals, and it changes when organs responsible for the elimination of the drug (i.e., kidney and liver) exhibit abnormalities. The absorption rate constant  $K_a$ , on the other hand, depends on the route of administration, the dosage form, and the formulation of a drug. And, for hydrophobic drugs or when the absorption is dissolution-rate-limited, the faster dissolution is generally reflected in the higher value for the absorption rate constant. Therefore, by changing the formulation of a drug or route of administration, one can alter the peak time and, thereby, the rate of absorption and time for the onset of action.

## B. Peak Plasma Concentration

The  $(C_p)_{\max}$  represents the highest drug concentration in the systemic circulation, or the plasma concentration that corresponds to the peak time. Furthermore, this parameter is often associated with the intensity of the pharmacological response of the drug. Therefore, the peak plasma concentration (see Fig. 1) of a drug following the administration of a dosage form should be above the minimum effective concentration (MEC) and below the minimum toxic concentration (MTC). The peak plasma concentration can depend on the absorption rate constant  $K_a$  and the fraction of the administered dose that eventually reaches the systemic circulation. The higher the absorption rate constant and fraction that reaches the general circulation, the greater is the peak plasma concentration for the administered dose. The route of administration, the dosage form, and the formulation, therefore, can influence the peak plasma concentration. It is determined by using Eq. (2):

$$(C_p)_{\max} = \frac{K_a F(X_a)_0}{V(K_a - K)} (e^{-K t_{\max}} - e^{-K_a t_{\max}}) \quad (2)$$

where:  $F$  is the fraction of the dose that eventually reaches the systemic circulation;  $(X_a)_0$  is the administered dose;  $V$  is the apparent volume of distribution of a drug; and,  $t_{\max}$  is the peak time. Because the term  $K_a F(X_a)_0/V$  ( $k_a - k$ ) in Eq. (2) constitutes the intercept of the plasma concentration-time profile, Eq. (2) can be written as

$$(C_p)_{\max} = I(e^{-K t_{\min}} - e^{-K_a t_{\max}}) \quad (3)$$

where:  $I$  is the intercept ( $\mu\text{g/mL}$ ) of the plasma concentration-time profile.

## C. Area Under the Plasma Concentration Time Curve

The AUC represents the extent of absorption of a drug following the administration of a dosage form. The greater the fraction of the dose that reaches the general circulation, the greater is the extent of the absorption; hence,  $(\text{AUC})_0^\infty$ . The term  $(\text{AUC})_0^\infty$ , expressed as micrograms per milliliter times hour ( $\mu\text{g mL}^{-1} \cdot \text{h}$ ) for a drug following its administration by various extravascular routes or various dosage forms that are administered extravascularly is determined by employing Eq. (4):

$$(\text{AUC})_0^\infty = \frac{K_a F(X_a)_0}{V(K_a - K)} \left[ \frac{1}{K} - \frac{1}{K_a} \right] \quad (4)$$

All the terms of Eq. (4) have been defined and can further be reduced to

$$(\text{AUC})_0^\infty = \text{Intercept} \left[ \frac{1}{K} - \frac{1}{K_a} \right]$$

The intercept in Eq. (5) bears a direct relationship to the time profile. The extent of absorption is given by (6).

$$(\text{AUC})_0^\infty = \frac{F(X_a)_0}{VK}$$

where, the term  $VK$  is the systemic clearance, a parameter being independent of the route of administration and the extravascularly administered dose. The extent of absorption [i.e.,  $(\text{AUC})_0^\infty$ ] of the administered dose reaches the systemic circulation [i.e.,  $F(X_a)_0$ ].

## III. FACTORS AFFECTING DRUG DISSOLUTION AND ABSORPTION

There are several factors responsible for drug dissolution and absorption. Broadly speaking, these factors are categorized into three groups: form-related, patient-related, and drug-related. Genetic characteristics, or gastric emptying time, on these factors is beyond the scope of this review.

Dosage form-related factors include particle size, related variables, such as porosity, surface area, and method of manufacturing, coating, etc.

The fact that the bioavailability of a drug is influenced by its physical state and the route of administration has been unequivocally demonstrated. For example, through dosage forms, these factors can be made complete and consistent bioequivalent.

Following the administration of a drug, a sequence of steps is required for its absorption. As shown in Fig. 2, an intact dosage form disintegration and deaggregation. The dissolved drug molecules are then absorbed and be picked up by the blood stream. The faster the drug molecules reach the systemic circulation, the greater is the bioavailability.

concentration in the systemic circulation corresponds to the peak time. Associated with the intensity of the peak, therefore, the peak plasma concentration after administration of a dosage form (MEC) and below the peak plasma concentration can be determined, and the fraction of the administered dose reaching the general circulation. The higher the administered dose, the more the drug reaches the general circulation, the more the administered dose. The route of administration, therefore, can be determined by using Eq. (2):

(2)

It eventually reaches the systemic circulation.  $V$  is the apparent volume of distribution. Because the term  $K_a F(X_a)_0 / V$  is the slope of the plasma concentration-time

(3)

plasma concentration-time profile.

### Plasma Concentration-Time Curve

After administration of a drug following the absorption, the fraction of the dose that is absorbed is the extent of the absorption; expressed as micrograms per milliliter following its administration by various routes that are administered extravas-

(4)

All the terms of Eq. (4) have been defined previously. Equation (4) can further be reduced to

$$(AUC)_0^\infty = \text{Intercept} \left[ \frac{1}{K} - \frac{1}{K_a} \right] \quad (5)$$

The intercept in Eq. (5) being the intercept of the plasma concentration-time profile. The extent of absorption can also be determined by using Eq. (6).

$$(AUC)_0^\infty = \frac{F(X_a)_0}{VK} \quad (6)$$

where, the term  $VK$  is the systemic clearance of the administered drug. This parameter being independent of the route of administration, the formulation, and the extravascularly administered dosage form, it is ostensible that the extent of absorption [i.e.,  $(AUC)_0^\infty$ ] is controlled by the product of the fraction of the administered dose reaching the general circulation and the administered dose [i.e.,  $F(X_a)_0$ ].

### III. FACTORS AFFECTING BIOAVAILABILITY: DISSOLUTION AND GRANULE PROPERTIES

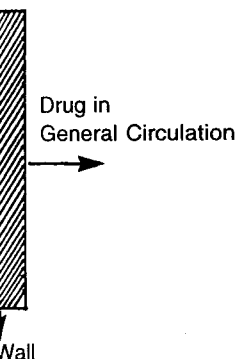
There are several factors responsible for the variation in bioavailability. Broadly speaking, these factors can be classified as patient-related or dosage form-related. Patient-related factors include age, disease state, abnormal genetic characteristics, or gastrointestinal physiology. The detailed discussion on these factors is beyond the scope of the objectives of this chapter.

Dosage form-related factors include formulation- and manufacturing-related variables, such as particle size, type and quantity of excipient used, method of manufacturing, compression pressure, and many other factors.

The fact that the bioavailability of a drug may be significantly affected by its physical state and the dosage forms by which it is administered has been unequivocally demonstrated. Also, because drugs are administered through dosage forms, these dosage forms should have adequate stability, complete and consistent bioavailability, and uniform composition.

Following the administration of a drug through a solid dosage form, a sequence of steps is required before the drug reaches the systemic circulation. As shown in Fig. 2, an orally administered solid dosage form undergoes disintegration and deaggregation, followed by the dissolution of the drug. The dissolved drug molecules must penetrate the gastrointestinal membrane and be picked up by the blood. Each of the steps involved may limit how fast the drug molecules reach the general circulation; therefore, its site of





s of the drug dissolution and its entry

esistance is referred to as the rate-  
ing, on the other hand, will depend  
dosage form and the physiology  
he discussion here, however, will  
e dosage form.

e form must disintegrate or deag-  
e for absorption. Drug dissolution  
anules. Therefore, the properties  
how dissolution is influenced by  
dosage form, whether or not a drug  
il it has dissolved into the luminal  
e of the effects of disintegration  
remaining discussion will focus  
of the drug.

compressed tablets are the ones  
obtained by using either wet gran-  
t granulation process consists of  
ial and wetting the mixture with  
a suitable binder, such as gelatin,  
he damp mass is passed through  
produce cohesive granules. Each

granule, in theory, is a blend of active ingredient and excipients. The granules flow readily through the hopper into the tablet press and are easily compressed.

Many processes used in the tablet manufacturing greatly influence the dissolution rates of active ingredient. The method of manufacture, the size, the moisture content, age and the flow property of the granules, the order of mixing of ingredients during the granulation, as well as the compression force employed in the tableting process, all contribute to the dissolution characteristics of the final product and, therefore, may affect the bioavailability of the drug from the finished product.

Several studies have demonstrated that the granulation process, in general, enhances the dissolution rate of poorly soluble drugs [1]. The use of dilutents and fillers, such as starch [2], anhydrous [3] and spray-dried lactose [4,5], microcrystalline cellulose [6], and compression force, particle size, and lubricants [7] tend to enhance the hydrophilicity of the active ingredients and improve their dissolution characteristics. For this, the wet granulation procedure was considered a superior method compared with other methods. However, the newer-tableting machines and excipients accompanied by careful formulation and proper mixing sequence, will permit preparation of tablets with good dissolution characteristics and not be dictated by the method of preparation per se.

Marlow and Shangraw [8] reported that sodium salicylate tablets prepared by direct compression with spray-dried lactose uniformly exhibited more rapid and complete dissolution, compared with those prepared by wet granulation. Furthermore, it was reported that the presence of disintegrant in the dry compression was essential for good dissolution. Finholt et al. [9] reported, in a separate comparative study, with phenobarbital tablets that were manufactured by both wet and dry granulation, that both procedures yielded comparable dissolution rates, provided a disintegrant was incorporated and mixed with the drug before dry granulation. However, the incorporation of disintegrant following the dry granulation of a drug resulted in slower dissolution rates.

In the manufacturing of tablets by the conventional wet granulation method, there are many independent factors that affect the property of granules and, therefore, the dissolution rate. The recent advances in granulation technology and the employment of high shear mixers and fluid bed granulating equipment have helped identify several critical in-process variables. The systematic control of variables, such as the type and time of mixing of the granules, time and temperature of drying, blending time with lubricant, age of the granules, moisture content of the granules at the time of compression, and the tablet crushing strength, are of importance to ensure the consistency in the dissolution and, thereby, the bioavailability.



In early studies on the physics of tablet compression, Higuchi et al. [10] recognized the influence of compressional forces employed in the tableting process on the apparent density, porosity, hardness, disintegration time, and average particle size of the compressed tablets. Hardness is a measure of resistance of a dosage form to mechanical deformation. It is a function of high-compression forces used in the manufacturing, and it may change with the aging of granules. Higuchi et al. [10] reported a linear relation between hardness and the logarithm of the compressional force; the specific surface of the compressed tablets underwent marked changes during the compressional process. The high compression may increase the specific surface and, hence, may enhance the dissolution. On the other hand, the high compression may also inhibit the wettability of a tablet owing to the formation of a firmer and more effective sealing layer of the lubricant resulting from the high pressure and temperature that accompany a strong compressional force. Levy et al. [2] reported that salicylic acid tablets, when prepared by double compression, showed an increase in the dissolution with an increase in the precompression pressure owing to fracturing of drug particles at higher pressure. The higher compression may also produce slower dissolution, at least in the initial period, because of an increased difficulty of fluid penetration into the compressed tablets. Luzzi et al. [11] and Jalsenjak [12] observed that the dissolution rate of sodium phenobarbital is inversely proportional to the hardness of the tablet or microcapsule.

Another important granule property that influences the dissolution of a drug is the moisture content of the granule at the time of compression. Chowhan et al. [13-17] studied the effect of moisture content and crushing strength on ticlopidine hydrochloride tablet friability and dissolution. At the moisture content of 1-2%, the drug dissolution was inversely related to the tablet crushing strength [16]. However, at the moisture content level of 3-4%, there was no clear relation between the dissolution and the crushing strength.

In later studies by Chowhan et al. [14,17], it was reported that granules prepared by high-speed shear mixer were less porous than those prepared by planetary mixer, and the porosity of the tablet may improve the dissolution of drug by facilitating solvent penetration, provided the entrapment of air in the pores is minimized or avoided.

In yet another important study, Levy et al. [2] studied the effect of the granule size on the dissolution rate of salicylic acid tablets and found that the dissolution rate increased with a decrease in the granule size; however, the increase in dissolution rate was not proportional to the increase in the apparent surface area of the granules. Furthermore, it was also reported that the dissolution rate decreased significantly with the increase in the age of the granules.

The chemical composition, which subsequently affects the dissolution rate, is another factor causing alteration in the dissolution rate of tablets. For example, in the case of hydrochlorothiazide tablets, granules stored at different temperatures ranging from room temperature to 40°C showed different dissolution rates. This was reflected in their *in vitro* dissolution. On the other hand, tablets granules did not show any change in dissolution rate.

#### IV. SUMMARY

Drug availability following oral administration depends on the following steps:

1. Getting the drug into the system
2. Moving the drug through the intestinal tract
3. Moving the drug into the general circulation

It is clear from the above discussion that the dissolution rate is especially for poorly soluble drugs, and it is affected by the site of administration, the drug properties, the drug dissolution properties, the drug properties and the drug properties. Knowledge of these factors will allow the formulation of a drug will allow the formulation of a drug by selecting the process in a proper manner.

#### ACKNOWLEDGMENT

The author would like to thank the University of Maryland for his assistance.

blet compression, Higuchi et al. onal forces employed in the tab- orosity, hardness, disintegration mpressed tablets. Hardness is a mechanical deformation. It is a n the manufacturing, and it may chi et al. [10] reported a linear n of the compressional force; the underwent marked changes during pression may increase the specific tion. On the other hand, the high ty of a tablet owing to the for- g layer of the lubricant resulting at accompany a strong compres- icyclic acid tablets, when prepared se in the dissolution with an in- ng to fracturing of drug particles n may also produce slower dis- use of an increased difficulty of s. Luzzi et al. [11] and Jalsenjak odium phenobarbital is inversely r microcapsule.

that influences the dissolution of nule at the time of compression. of moisture content and crushing friability and dissolution. At the tion was inversely related to the the moisture content level of 3— the dissolution and the crushing

[17], it was reported that granules less porous than those prepared e tablet may improve the disso- stration, provided the entrapment d.

et al. [2] studied the effect of the icyclic acid tablets and found that ase in the granule size; however, roportional to the increase in the nermore, it was also reported that y with the increase in the age of

The chemical components of the formulation also prolong disintegration time, which subsequently affects the drug dissolution and bioavailability. Inert fillers potentiate the chemical degradation of active ingredient, causing alteration in the disintegration and dissolution time of compressed tablets to change with storage. Alam and Parrott [18] have shown that hydrochlorothiazide tablets, granulated with acacia and stored at temperatures ranging from room temperature to 80°C increased in hardness with time. This was reflected in their increased disintegration and dissolution time. On the other hand, tablets granulated with starch and polyvinyl pyrrolidone did not show any change in disintegration and dissolution time.

#### IV. SUMMARY

Drug availability following the oral dosing may be thought of as the resultant of the following steps:

1. Getting the drug into solution
2. Moving the drug molecules through the membrane of the gastrointestinal tract
3. Moving the drug away from the site of administration into the general circulation

It is clear from the discussion that the bioavailability of drugs, especially for poorly soluble drugs, depends mainly on the ability of the drug to dissolve at the site of administration. The dissolution, in turn, especially from solid dosage forms, such as tablets and capsules, depends on the granule properties and the processing variables used in their manufacture. The granule properties and other variables that determine and influence the granule properties will serve as major topics of discussion in other chapters. Knowledge of these factors and their role in influencing the bioavailability of a drug will allow the formulators to develop an optimum drug dosage form by selecting the process and preparation variables involved in a rational manner.

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## REFERENCES

1. S Solvang, P Finholt. Effect of tablet processing and formulation factors on dissolution rates of active ingredient in human gastric juice. *J Pharm Sci* 59: 49-52, 1970.
2. G Levy, J Antkowiak, J Procknal, D White. Effect of certain tablet formulation factors on dissolution rate of the active ingredient II: granule size, starch concentration, and compression pressure. *J Pharm Sci* 52:1047-1051, 1963.
3. N Batuyios. Anhydrous lactose in direct tablet compression. *J Pharm Sci* 55: 727-730, 1966.
4. W Gunsell, L Lachman. Comparative evaluation of tablet formulations prepared by conventionally processed and spray dried lactose. *J Pharm Sci* 52:178-182, 1963.
5. R Duvall, K Koshy, R Dashiell. Comparative evaluation of dextrose and spray dried lactose in direct compression systems. *J Pharm Sci* 54:1196-1200, 1965.
6. G Reier, R Shangraw. Microcrystalline cellulose in tableting. *J Pharm Sci* 55: 510-514, 1966.
7. T Iranloye, E Parrott. Compression force, particle size, and lubricants on dissolution rates. *J Pharm Sci* 67:535-539, 1978.
8. E Marlow, R Shangraw. Dissolution of sodium salicylate from tablet matrices prepared by wet granulation and direct compression. *J Pharm Sci* 56:498-504, 1967.
9. P Finholt, P Pedersen, R Solvang, K Wold. *Medd Norsk Farm Selsk* 28:238, 1966.
10. T Higuchi, A Rao, E Busse, J Swintosky. The physics of tablet compression II: the influence of degree of compression on properties of tablets *Am Pharm Assoc Sci Ed* 42:194-200, 1953.
11. L Luzzi, M Zoglio, H Maulding. Preparation and evaluation of the prolonged release properties of nylon microcapsules. *J Pharm Sci* 59:338-341, 1970.
12. I Jalsenjak, C Nicolaidou, J Nixon. Dissolution from tablets prepared using ethylcellulose microspheres. *J Pharm Pharmacol* 29:169-172, 1977.
13. ZT Chowhan, L Palagyi. Hardness increase induced by partial moisture loss in compressed tablets and its effect on in vitro dissolution. *J Pharm Sci* 67: 1385-1389, 1978.
14. ZT Chowhan. Moisture, hardness, disintegration and dissolution interrelationships in compressed tablets prepared by the wet granulation process. *Drug Dev Ind Pharm* 5:41-62, 1979.
15. ZT Chowhan. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on in vitro disintegration and dissolution. *J Pharm Sci* 69:1-4, 1980.
16. Z Chowhan, I Yang, A Amaro, L Chi. Effect of moisture and crushing strength on tablet friability and in vitro dissolution. *J Pharm Sci* 71:1371-1375, 1982.
17. Z Chowhan, B Chatterjee. A method for establishing in process variable controls for optimizing tablet friability and in vitro dissolution. *Int J Pharm Technol Prod Manuf* 5(2):6-12, 1984.

18. AS Alam, EL Parrott. Effect of moisture on the dissolution of chlorothiazide tablets. *J Pharm Sci* 55: 727-730, 1966.

## RECOMMENDED READING

- Abdou HM. Dissolution, Bioavailability, and Drug Release. New York: Academic Press, 1989.
- Blanchard J, R Sawchuk, B Brodeur. *Drug Bioavailability*. Basel: S Karger, 1989.
- Gibaldi M. *Biopharmaceutics and Pharmacokinetics*. Lea & Febiger, 1991.
- Leeson LJ, J Carstensen, eds. *Drug Bioavailability*. New York: Marcel Dekker, 1989.
- Stavchansky SA, JW McGinity. *Drug Bioavailability in Tablet Technology*. Vol 2. 2nd ed. New York: Marcel Dekker, 1989.

18. AS Alam, EL Parrott. Effect of aging on some physical properties of hydrochlorothiazide tablets. *J Pharm Sci* 60:263-266, 1971.

## RECOMMENDED READING

- Abdou HM. Dissolution, Bioavailability and Bioequivalence. Easton PA: Mack Publishing, 1989.
- Blanchard J, R Sawchuk, B Brodie, eds. Principles and Perspectives in Drug Bioavailability. Basel: S Krager, 1979.
- Gibaldi M. Biopharmaceutics and Clinical Pharmacokinetics. 4th ed. Philadelphia: Lea & Febiger, 1991.
- Leeson LJ, J Carstensen, eds. Dissolution Technology. Washington DC: Academy of Pharmaceutical Sciences, 1974.
- Stavchansky SA, JW McGinity. In: HA Lieberman, L Lachman, JB Schwartz, eds. Bioavailability in Tablet Technology Pharmaceutical Dosage Forms: Tablets. Vol 2. 2nd ed. New York: Marcel Dekker, 1990.

# 16

## Regulatory Issues in Granulation Processes

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## I. INTRODUCTION

Any discussion of regulatory issues can at best be considered a snapshot. As this text is being prepared, international guidelines affecting pharmaceutical manufacturing are in draft, the US Food and Drug Administration (FDA) is transforming its basic office level drug review structure, and the US Congress, under consumer pressure to quicken the drug approval process, is threatening legislative restructuring that would shift some review authority away from the central FDA offices. The effect this will have on drugs currently in development that will be marketed long after these changes occur, is impossible to determine. Perhaps the best protection against major redevelopment is a solid, scientifically defensible approach to new product development. A discussion of the potential influence of regulatory change on the drug manufacturing environment should aid in arriving at that defensible approach.

## II. INTERNATIONAL HARMONIZATION OF GOOD MANUFACTURING PRACTICES

The concept of adhering to current good manufacturing practices (cGMP) is well ingrained in the US pharmaceutical manufacturing environment. Control of raw materials, in-process goods, packaging and labeling materials, and finished products; documentation of processes to ensure those controls are effectively executed and that manufacturing processes are reliably reproduced are ideas familiar to every development scientist. Interpretation of the adequacy of these procedures and controls is subject to ongoing review and change. As globalization of the world economy advanced, dissimilarities were noted across international boundaries in the interpretation of what entailed adequately controlled pharmaceutical-manufacturing processes. The move toward global harmonization of manufacturing processes is rapidly becoming a reality.

### A. US Good Manufacturing Practices

Current good manufacturing practices (cGMPs) for pharmaceuticals are defined by US regulation in 21CFR Parts 210 and 211 and have been modified,

interpreted, and extended through various regulatory guidelines, guidances, and monographs. These outline basic principles of manufacturing, not only the manufacture, but also the organization, process, and equipment.

Of particular interest to the pharmaceutical industry are the requirements for appropriate sampling of granulated products [1]. These regulatory requirements, which include procedures to sample, test, and verify uniformity, and homogeneity, and purity as appropriate. In the intermediate, the properties of the granules, and the properties, it is appropriate to consider the granulation process for the granulation process, that sampling for such intermediate dosage form [2].

In-process specification analysis of process variability, average outcomes. At the end of the process is presumably less understood, large, and specifications are better understood, variability, regulatory requirements is established based on the improvement, then "tighten" the in-process specification. If this process lead to a specification so narrow production.

What is an appropriate specification? Given the complexity of dissolution, and other physical properties, one can statistically determine a process that will not drive the process. Documentation of this exercise to stop reducing in-process variability.

### B. ICH Guidelines

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) identify and reduce differences in regulatory development in the three primary areas of quality, safety, and efficacy.

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at best be considered a snapshot. Guidelines affecting pharmaceutical guidelines affecting pharmaceutical Food and Drug Administration drug review structure, and the quicken the drug approval process that would shift some review processes. The effect this will have on products to be marketed long after these changes. Perhaps the best protection scientifically defensible approach to the potential influence of regulatory environment should aid in arriving

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manufacturing practices (cGMP) manufacturing environment. Controlling packaging and labeling materials, processes to ensure those controls manufacturing processes are reliably re-evaluated by scientist. Interpretation of controls is subject to ongoing review economy advanced, dissimilarities in the interpretation of what essential-manufacturing processes. The manufacturing processes is rapidly

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MPs) for pharmaceuticals are defined in 211 and have been modified,

interpreted, and extended through a multiplicity of communications, including guidelines, guidances, and regulatory letters, among others. The cGMPs outline basic principles of manufacturing finished pharmaceuticals, including not only the manufacture, testing, documentation, and release of products, but also the organization, personnel, and the physical design of facilities.

Of particular interest to the granulation process are the cGMP requirements for appropriate sampling and testing of in-process materials and drug products [1]. These regulations require the establishment of written procedures to sample, test, and validate processes to assure adequacy of mixing, uniformity, and homogeneity, and to establish the identity, strength, quality, and purity as appropriate. Because the granulation step results in a finite intermediate, the properties of which largely dictate the final product properties, it is appropriate to establish significant in-process tests and specifications for the granulation product. The FDA has proposed a rule requiring that sampling for such intermediates approximate the size of the finished dosage form [2].

In-process specifications should be established based on a statistical analysis of process variability estimates and previous acceptable process average outcomes. At the early developmental stage, when process control is presumably less understood, it is reasonable for process variability to be large, and specifications are often set very wide. As the process becomes better understood, variability must be reduced. One interpretation of the regulatory requirements is that in-process specifications must be reestablished based on the improved variability of the process. The tendency is to then "tighten" the in-process controls to operate well within this revised specification. If this process is executed iteratively, this interpretation may lead to a specification so narrow that it requires singular point process reproduction.

What is an appropriate point at which to stop narrowing in-process specifications? Given the compendial tolerances for variability in content, dissolution, and other physical tests results, and the final product variability, one can statistically determine the allowable variability in the granulation process that will not drive the final product outside its acceptable ranges. Documentation of this exercise can provide a defensible position from which to stop reducing in-process control limits.

## B. ICH Guidelines

The International Conference on Harmonization (ICH) was organized to identify and reduce differences in technical requirements for drug product development in the three principal global registration regions: the European

Union, Japan, and the United States [3]. The ICH is sponsored by both regulatory and pharmaceutical-manufacturing interests from these regions whose common goals include global registration of products. To date, ICH has published guidance on various aspects of the development process, particularly in the areas of preclinical pharmacology and toxicology, pharmacokinetics, stability testing, general registration requirements, and others. Although these guidances have not been directed at in-process products, such as granulation, their direction virtually dictates adequate documentation, testing, specification development, and validation similar to those required by cGMPs. The scientist formulating international products should focus attention on documenting all aspects of the manufacturing and testing processes, and plan to reconcile those documents with future recommendations from ICH.

### C. ISO 9000 Standards

The International Organization for Standardization (ISO), based in Geneva, Switzerland, is a multinational organization comprising more than 90 industrialized nations, whose goal is to promote quality standardization within industries to facilitate international trade on a level playing field [4]. ISO 9000 certification indicates that a company's policies, procedures and standards are sufficient to assure the consistent quality of its products. Such certification has already become a must for companies selling excipients internationally. Likewise, bulk drug suppliers to manufacturers of multi-source drug products may find ISO certification a competitive necessity; however, manufacturers of finished drug products, especially those with local patent protection, will likely not need ISO certification.

What are the ISO 9000 requirements? This is actually a series of five documents: ISO 9000 is an overview document designed to aid companies in deciding which quality standard is appropriate for their products. ISO 9004 is a separate document describing how to implement and manage the ISO 9000 series certification. The three levels of ISO certification are detailed in documents ISO 9001 through 9003.

- ISO 9001 is the most stringent and thus most difficult certification to obtain. It describes quality standards for product design, development, manufacturing, inspection, and testing.
- ISO 9002 describes the intermediate level of ISO certification and covers primarily manufacturing, inspection, and testing.
- ISO 9003 describes the easiest ISO certification to obtain and addresses inspection and testing standards.

The US cGMP compliance, according to FDA guidance, has an 85–90% overlap in GMPs. ICH does not note significant differences between US and ICH GMP compliance is a requirement for quality program. ICH provides for quality program with defined roles for management and continuous improvement. ISO 9000 includes statistical trend analyses. Certification (QC–QA) group handles controls, and that is retained by cGMPs, too, require numerous operations, versus more general guidelines does not necessarily.

### III. SCALE-UP CONSIDERATIONS

Scale-up of granulation process theory applies only minimally. It is possible to apply in such cases density, cohesiveness, and other processes involves not only changes in physical configuration and batch size that occurred before, but also changes in process. Hence using the small-scale process changes, likewise required regulatory approval without exception. For these reasons, FDA in 1994, Pharmaceutical Scientists (PAC) and postapproval changes task force, as they pertain to the United States, were published as a guideline in late 1994 [7]. If binding, this interim guideline would require requirements for changes in manufacturing scale, or manufacturing process.

#### A. Composition Changes

In composing the SUPAC guidelines, FDA recognized that all changes



The ICH is sponsored by both regulatory interests from these regions and industry. To date, ICH covers all aspects of the development process, including pharmacology and toxicology, pharmaceutical development requirements, and others. It is directed at in-process products, and it dictates adequate documentation and validation similar to those required for international products should they be marketed. The manufacturing and testing requirements with future recommenda-

ization (ISO), based in Geneva, Switzerland, comprising more than 90 international quality standardization within a level playing field [4]. ISO's policies, procedures and standards ensure the quality of its products. Such standards are a competitive necessity; for companies selling excipients to manufacturers of multi-dose products, especially those with ISO certification.

This is actually a series of five standards designed to aid companies in developing appropriate for their products. ISO standards allow to implement and manage the various levels of ISO certification are described in Table 3.

and thus most difficult certification standards for product design, development, and testing. The level of ISO certification and inspection, and testing. ISO certification to obtain and adhere to standards.

The US cGMP compliance is generally equivalent to ISO 9001 according to FDA guidance and interpretation [5]. Industry analysts suggest an 85–90% overlap in GMP and ISO 9001 requirements, but are quick to note significant differences do exist. ISO is a voluntary program, whereas GMP compliance is a requirement (at least in the United States). ISO provides for quality program generalities, such as a *Quality Manual*, with defined roles for management in the quality process, and a program of continuous improvement. ISO also requires specifics not in GMPs, such as statistical trend analyses. GMPs require that the quality control–quality assurance (QC–QA) group be separate from the manufacturing group it controls, and that it retains complete responsibility for product release. The GMPs, too, require numerous specifics, such as double signatures on key operations, versus more generalities in ISO. Compliance with either set of guidelines does not necessarily imply compliance with the other.

### III. SCALE-UP CONSIDERATIONS

Scale-up of granulation processes is often technically troublesome. Mixing theory applies only minimally to mixed-phase systems, and is nearly impossible to apply in such cases when assumptions of uniform particle size, density, cohesiveness, and others are invalid. Scale-up of granulation processes involves not only changes in size, but often equipment of different physical configuration and even operating principle. Historically, changes in batch size that occurred before marketing were often tested for bioequivalence using the small-scale clinical batch as a standard. Postmarketing scale changes, likewise required some direct measure of bioequivalence and prior regulatory approval without regard to the type of drug or process in question. For these reasons, FDA in association with the American Association of Pharmaceutical Scientists (AAPS), formed a task force to address scale-up and postapproval changes (SUPAC) in drug products. The findings of that task force, as they pertain to immediate-release solid oral dosage forms in the United States, were published in the trade press in 1993 [6], as an interim guideline in late 1994 [7], and in final form in 1995 [8]. Although not binding, this interim guideline provides substantial insight into the regulatory requirements for changes in components or composition, manufacturing site, manufacturing scale, or manufacturing processes.

#### A. Composition Changes

In composing the SUPAC guidelines, FDA, industry, and academic scientists recognized that all changes cannot be considered equally. Changes are con-

**Table 1** SUPAC Level Component or Composition Change Levels

Excipient	% Excipient (w/w of total dosage unit)		
	Level 1	Level 2	Level 3
Filler	$\pm 5$	$\pm 10$	$>10$
Disintegrant			
Starch	$\pm 3$	$\pm 6$	$>6$
Other	$\pm 0.5$	$\pm 1$	$>2$
Binder	$\pm 0.5$	$\pm 1$	$>1$
Lubricant			
Ca or Mg	$\pm 0.25$	$\pm 0.5$	$>0.5$
Stearate			
Other	$\pm 1$	$\pm 2$	$>2$
Glidant			
Talc	$\pm 1$	$\pm 2$	$>2$
Other	$\pm 0.1$	$\pm 0.2$	$>0.2$
Film coat	$\pm 1$	$\pm 2$	$>2$
Total drug recipient	5	10	n/a
Change (%)			

Source: Ref. 6.

sidered relative to their potential influence on the drug product and are ranked in various action levels. Level 1 "... is reserved for changes that are unlikely to have any detectable impact on the formulation quality and performance" [8]. Level 2 changes are moderate changes that could have a significant effect on final product quality and performance. Level 3 changes are those most likely to have a significant effect on the formulation quality and performance and essentially captures all changes that do not fall into level 1 or 2. All level 3 changes require full bioequivalence testing. Implementation requires prior approval.

Table 1 summarizes composition changes by level. It is important to recognize that none of the changes in any level are allowed to exceed the validated range of ingredients specified in the application. For this reason, it is suggested that the formulation scientist establish valid ranges of excipient concentrations as wide as possible before submission, to potentially avoid a full bioequivalence study with future minor excipient changes.

## B. Dissolution-Testing Requirements

Dissolution-testing requirements are added with level 2 composition changes and differ for drugs of differing characteristics. At level 2, the guideline

makes distinctions in changeability, and permeability of the drug is defined as narrow or specified in the guideline. It is based on the largest dose so (pH of minimum solubility) mL (low). High permeability absorption, in the absence of tract, greater than 90% or determined experimentally' categories and specifications for

It is important to the appropriately categorize a process. Characterization of may be appropriate early in trials will be available when comparisons.

## C. Site, Equipment, and

Other changes addressed in process changes, and identify categories listed in the foreground under each category by level bioequivalence testing as well

## D. Reporting Requirements

Two important documents manufacturing processes. The Drug Applications (NDAs), and nonsterile Abbreviated Applications changes that must be reported categories of reporting. The sections for reporting those changes controls section of annual reports changes in light of the record

Before the guideline, changing manufacturing could be changes that may or may not interim guidance document in the trade press [11]. Brief

## Composition Change Levels

w/w of total dosage unit)

Level 2	Level 3
±10	>10
±6	>6
±1	>2
±1	>1
±0.5	>0.5
±2	>2
±2	>2
±0.2	>0.2
±2	>2
10	n/a

on the drug product and are  
... is reserved for changes that  
t on the formulation quality and  
derate changes that could have a  
nd performance. Level 3 changes  
effect on the formulation quality  
all changes that do not fall into  
all bioequivalence testing. Imple-

anges by level. It is important to  
level are allowed to exceed the  
the application. For this reason,  
t establish valid ranges of excip-  
before submission, to potentially  
are minor excipient changes.

s

with level 2 composition changes  
istics. At level 2, the guideline

makes distinctions in change category, based on the therapeutic range, solubility, and permeability of the drug substance. The therapeutic range of the drug is defined as narrow or nonnarrow, with narrow therapeutic range drugs specified in the guideline. Drug solubility is defined as either high or low, based on the largest dose solubility volume (at the physiologically attainable pH of minimum solubility) of less than 250 mL (high) and more than 250 mL (low). High permeability drugs are "generally those with an extent of absorption, in the absence of documented instability in the gastrointestinal tract, greater than 90% or those whose permeability attributes have been determined experimentally" [8]. Table 2 lists the dissolution testing categories and specifications for each.

It is important to the formulation scientist or dissolution chemist to appropriately categorize a new drug substance early in the development process. Characterization of a pivotal biobatch by case B dissolution criteria may be appropriate early in the development process, so that historical controls will be available when later scale-up events require dissolution comparisons.

### C. Site, Equipment, and Process Changes

Other changes addressed in the guideline include site, equipment, and process changes, and identify requirements for each in terms of the dissolution categories listed in the foregoing. Table 3 summarizes the changes permitted under each category by level and describes the chemistry, dissolution, and bioequivalence testing as well as documentation requirements.

### D. Reporting Requirements

Two important documents address reporting requirements for changes in manufacturing processes. The first, a draft guideline on supplements to New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and nonsterile Abbreviated Antibiotic Drug Applications (AADA) [9] describes changes that must be reported before implementation as well as other categories of reporting. The second, a guidance letter [10], describes requirements for reporting those changes in the chemistry, manufacturing, and controls section of annual reports. Both of these documents address reporting changes in light of the recommendations from the SUPAC discussions.

Before the guideline, the most complete discussion of changes affecting manufacturing could be found in 21CFR 314.70(b), which discusses changes that may or may not be initiated before FDA approval, and in an interim guidance document issued by FDA in late 1994 [7] and summarized in the trade press [11]. Briefly, any change that served to improve the quality

Table 2 SUPAC-Defined Dissolution Testing Categories

Dissolution category	Applicable to drugs	Medium	Time points (min)	Specification
Case A	↑ Permeability/ ↑ solubility	0.1N HCl	15	85%
Case B (perform case A studies plus)	↑ Permeability/ ↓ solubility, or ↓ permeability/ ↑ solubility	Water 0.1N HCl pH4.5, pH 6.5, pH 7.5 (plus surfactant if justified)	15, 30, 60, 120, 180	90% or asymptote is reached; profile similar to current product
Case C	Site changes	Application/ compendial medium	15, 30, 60, 120, 180, or until asymptote is reached	Profile similar to current product

Source: Ref. 6.

of the product by adding methods, facilities, or controls without prior approval. With the inclusion of changes in compendial testing regulatory analytical methods in the manufacture. Based in part on the findings, FDA has reclassified

With the ability to monitor and assure that those changes are properly documented. That responsibility to justify, validate, and document the changes. Detailed accounts of these procedures that direct their operations with clarity equal to the

The FDA has also developed reports pertaining to formulation changes [10]. Manufacturing changes in compendial testing, position, expiration dating, and analytical methods. The revalidation sample submission documents

E. Summary

It may be of critical importance in bioequivalence testing is a scientist should consider the operating principle, and in the biobatch product to maximize characteristics require treating, possibly including scaling production, may avoid replication

IV. CLINICAL SUPPLIES

Clinical supplies manufacturing development process, when the supply is small and its consumption

Case C	Site changes	Application/ compendial medium	15, 30, 60, 120, 180, or until asymptote is reached	Profile similar to current product
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Source: Ref. 6.

of the product by adding specifications or test method, or changing the methods, facilities, or controls used in release of that product were allowed without prior approval. Virtually any other change required prior approval, including changes in composition, relaxing specification limits, adding or deleting regulatory analytical specifications, and changing the method or site of manufacture. Based in part on the outcome of the SUPAC committee meetings, FDA has reclassified manufacturing changes, as shown in Table 4.

With the ability to make such changes, comes the responsibility for assuring that those changes are justified and their effects on the product documented. That responsibility falls directly on the pharmaceutical manufacturers' validation and quality assurance groups, who will shoulder greater responsibility to justify, validate, and document manufacturing changes [10]. Detailed accounts of these processes, and the internal change control procedures that direct their outcomes should be provided to regulatory authorities with clarity equal to that of the data itself.

The FDA has also detailed the format and content expected in annual reports pertaining to formulation and testing in a guidance released in early 1995 [10]. Manufacturing changes are notably absent from this document. This guidance is a straightforward listing of the requirements for the CMC section of the annual report and specifies requirements for compliance, with changes in compendial test methods and specifications, formulation composition, expiration dating, container closure systems, and noncompendial analytical methods. The reader is directed to the guidance documents for sample submission documents.

## E. Summary

It may be of critical importance to develop a process such that frequent bioequivalence testing is avoidable. Therefore, the process development scientist should consider production equipment size, design, configuration, operating principle, and installation site before the production of pivotal biobatch product to maximize this potential. In the event that a drug's characteristics require treating all changes as level 3 changes, appropriate planning, possibly including scale-up and complete validation before biobatch production, may avoid repeated, expensive bioequivalence testing.

## IV. CLINICAL SUPPLIES MANUFACTURE

Clinical supplies manufacturing often occurs very early in the product development process, when the available quantity of drug substance is alarmingly small and its consumption for noncritical development steps is dis-

**Table 3** SUPAC-Defined Site Equipment and Process Change Requirements by Category

Type/level	Change permitted	Exclusions	Documentation			
			Chemistry	Dissolution	Bio-equivalence	Filing
Component or composition						
Level 1	Table 1 total change ≤ 5%	No change beyond approved target ranges	LTSS <sup>a</sup> commitment	Application/compendial only	None	Next annual report
Level 2	Table 1 total change ≤ 10%	No narrow therapeutic range drugs	Accelerated stability data plus LTSS commitment	Varies, see Table 2	None	Prior approval supplement
Level 3	Table 1	None	Accelerated stability data plus LTSS commitment	Case B, see Table 2	Full	Prior approval supplement
Site change						
Level 1	Contiguous campus	No scale or process changes	None	Application/compendial only	None	Change being effected supplement
Level 2	Different campus	No scale or process changes	Accelerated stability data and LTSS commitment	Case C, see Table 2	None	Change being effected supplement
Scale-up						
Level 1	≤ 10-fold increase in batch size	No change in site, controls, or equipment	LTSS commitment	Application/compendial only	None	Annual report notification of change and new batch records
Level 2	> 10-fold increase in batch size	No change in site, controls, or equipment	Accelerated stability data and LTSS commitment	Case C, see Table 2	None	Change being effected, new batch records
Manufacturing equipment						

Level 3	Table 1	None	commitment Accelerated stability data plus LTSS commitment	Case B, see Table 2	Full	Prior approval supplement
Site change						
Level 1	Contiguous campus	No scale or pro- cess changes	None	Application/ compendial only	None	Change being ef- fected supple- ment
Level 2	Different campus	No scale or pro- cess changes	Accelerated stability data and LTSS commitment	Case C, see Table 2	None	Change being ef- fected supple- ment
Scale-up						
Level 1	≤ 10-fold increase in batch size	No change in site, controls, or equipment	LTSS commit- ment	Application/ compendial only	None	Annual report no- tification of change and new batch records
Level 2	> 10-fold increase in batch size	No change in site, controls, or equipment	Accelerated stability data and LTSS commitment	Case C, see Table 2	None	Change being ef- fected, new batch records
Manufacturing equipment						
Level 1	Non-to-automated/ non-to-mechanical; new equipment design w/wo same capacity	No change in operating principle	LTSS commit- ment	Application/ compendial only	None	Change being ef- fected, new batch records
Level 2	New design or oper- ating principle	None	Accelerated stability data and LTSS commitment	Case B, see Table 2	None	Prior approval supplement with change justification
Process						
Level 1	Operating outside validation ranges	None	LTSS commit- ment	Case C, see Table 2	None	Change being ef- fected supple- ment
Level 2	New process (e.g., wet-to-dry granu- lation)	None	Accelerated stability data and LTSS commitment	Case C, see Table 2	Full	Prior approval supplement with change justification

\*LTSS, long-term stability study.

Source: Ref. 7.

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Regulatory Issues in Granulation Processes

**Table 4** Reporting Requirements for Manufacturing Changes

Type of change	Prior approval	Annual report
Manufacturing with equipment change	a. Different operating procedure b. Basic methodology (tray to fluid bed drying)	a. Similar equipment b. Capacity change not more than 10 times
Reprocessing	Specification failures	Single-step repeats (drying, filtering, milling, blending)
Facilities*	Different facility where: a. process is materially different, b. new facility has not been cGMP qualified (including relocation where process changes significantly)	Simple relocations within an existing facility in which: 1. Process is materially the same. 2. New facility is cGMP qualified. 3. New equipment location. 4. Adding interior partitions to improve environmental control. 5. Replacing surfaces to enhance cleaning. 6. Replace or add lighting.

\*Facilities changes also include a third category for a change in manufacturing site in which the process does not materially differ from the approved process and the new facility has been cGMP inspection within the preceding 2 years. Under such conditions, a supplemental report is required before the annual report, but preapproval for implementation is not required.

Source: Ref. 8.

couraged. Under these nonroutine-manufacturing conditions, appropriate process characterization, or perhaps validation, is impossible to conduct. The FDA recognizes that early clinical studies may require production of small quantities of materials for human consumption that do not meet the minimum cGMP requirements for drug products [12]. With that in mind, FDA has issued guidelines [13] that provide principles and practices of general applicability that would aid in establishing some minimal level of acceptable GMP compliance for the manufacture of clinical supplies. In general, the guidelines provide for increased in-process and final product testing to assure the identity, purity, and uniformity of the finished product in the absence of validated processes and appropriate in-process controls.

## A. Design, Construction

The GMP requirements for some materials is generally waived, acknowledging that such physical space available. Labeling each number, batch number, and identification of each piece of equipment be avoided if the equipment the room bears clinical batch component control numbers must records.

## B. Component and In-P

Prospective written procedure approval of components and relation (14), is likewise avoided. Comprehensive final specifications to meaningfully establish, the identification through labeling for these requirements. Data establishment of in-process control

## C. Written Procedure Re

The requirements for complete and process controls may be unique identification number actual procedures employed long as the records collected quality control unit. In-process dictates, with data collected ment of in-process specificat

## D. Other Clinical Supply

Adequate records of component batch potentially affected by general requirements of the lecting data, rather than meet small clinical batch sizes can



Manufacturing Changes

Annual report	
a.	Similar equipment
b.	Capacity change not more than 10 times
	Single-step repeats (drying, filtering, milling, blending)
	Simple relocations within an existing facility in which:
1.	Process is materially the same.
2.	New facility is cGMP qualified.
3.	New equipment location.
4.	Adding interior partitions to improve environmental control.
5.	Replacing surfaces to enhance cleaning.
6.	Replace or add lighting.

a change in manufacturing site in which improved process and the new facility has s. Under such conditions, a supplemental approval for implementation is not required.

manufacturing conditions, appropriate ion, is impossible to conduct. The may require production of small tion that do not meet the mini- ts [12]. With that in mind, FDA inciples and practices of general some minimal level of acceptable clinical supplies. In general, the and final product testing to assure inished product in the absence of cess controls.

A. Design, Construction, and Equipment

The GMP requirements for separation of quarantined, approved, and rejected materials is generally waived in the clinical supply manufacturing area, acknowledging that such physical separation may be impossible with limited space available. Labeling each container with its contents by name or code number, batch number, and approval status will suffice. Likewise, identification of each piece of equipment as in-process for a particular batch can be avoided if the equipment is located in a controlled-processing room and the room bears clinical batch identification. Equipment identity and component control numbers must be duly noted in the clinical batch production records.

B. Component and In-Process Controls

Prospective written procedures describing the storage, sampling, testing, and approval of components and drug product containers, as required by regulation (14), is likewise avoidable. In recognizing that accurate and comprehensive final specifications for clinical components is often impossible to meaningfully establish, the FDA guideline allows for the use of appropriate identification through labeling, along with ongoing data collection, to suffice for these requirements. Data collected should be used for the future establishment of in-process controls.

C. Written Procedure Requirements

The requirements for complete prospective written batch production records and process controls may be circumvented. Clinical batch records with a unique identification number that accurately reflects component usage and actual procedures employed in the manufacturing process are sufficient, as long as the records collected are suitable for review and approval by the quality control unit. In-process testing is required as good scientific practice dictates, with data collected to provide background for eventual establishment of in-process specifications.

D. Other Clinical Supply Manufacturing Requirements

Adequate records of component usage should be kept so that every clinical batch potentially affected by a given component can be identified [15]. Other general requirements of the regulations can similarly be addressed by collecting data, rather than meeting a predefined specification. Yield losses with small clinical batch sizes can be excessive compared with those at full-scale

production. Reporting the actual yield is required, as is full accountability of losses incurred during manufacture, processing, and packaging. Reconciliation of all finished materials, including usable product distributed, used, returned, and destroyed is also required.

## V. GRANULATION PROCESS VALIDATION

Validating the granulation process is often included as a part of the overall validation process and should include the unit operations associated with granulation. If the granulation step involves an aqueous granulating agent, the water system validation should proceed first, but will not be addressed here. Dry blending and wet granulation steps usually occur in a single-unit operation, but uniformity (at a minimum) needs to be validated separately. Drying should be addressed as a singular process (except in fluid bed granulation processes), and final sizing must not be overlooked.

### A. Dry Blending and Wet Granulation

It is important to recognize that the granulation process was developed to overcome the difficulties inherent in handling powders of often widely differing physical properties. Physical mixing of such powders is often incomplete, and stable uniform mixtures are often impossible to handle without inherent physical segregation driven by differences in particle size, shape, density, and cohesiveness. Validation acceptance specifications should recognize this. Unit-of-use content uniformity often cannot be attained to the same degree in the dry-blending process, nor maintained in the interim-handling process before wet granulation, as would be required for finished product release. Interestingly, an FDA inspection guide [16] discusses this eventuality, but insists on unit-of-use sampling at the dry blend stage. Near unit-of-use sampling is a must and will typically require a specially sized sample thief. If final product uniformity cannot be attained at the dry blend stage, this should be clearly addressed in the validation plan, and supported with data detailing the physical limitations to absolute uniformity. Most importantly, meaningful specifications for attainable uniformity should be established and documented in the validation protocol. The final validation report should address the reliability with which finished tablets meet uniformity requirements when the dry blend varies within its uniformity specification.

This FDA field inspection guide [16] addresses various mixer types in terms of method of operation, design limitations, and standards of practice implemented to overcome these limitations. These are outlined in Table 5.

**Table 5** FDA-Recognized Mixer Types

Mixer type	Design features
Planetary (pony)	Open top Horizontal mixing Blade clearance Top loader
Ribbon blender	Discharge valve Blade clearance
Tumbler blender	Mixer volume Shaft packing Mixer volume Tumbling power
High shear	High-energy mixing Heat Chopper

Source: Ref. 15.

Before any blending validation is performed, the validation protocol must be established.

Following the same logic, the goals of binding these physical properties, the finished granulation must meet the validation specifications. The validation protocol must address the uniformity requirements for the granulation process.

### B. Drying

Two modes of drying are used in fluid bed dryers. Obviously, in validating a drying cycle, the uniformity, owing to the static tray loading. Tray loading is a critical factor in the validation of the drying process.

Although less obvious, fluid bed drying processes yield more difficult to compress tablets. The validation of the drying process must address the differences in compression characteristics. These processes are fully explored.

required, as is full accountability processing, and packaging. Reconstitutable product distributed, used,

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included as a part of the overall unit operations associated with an aqueous granulating agent, and first, but will not be addressed. Steps usually occur in a single-unit process needs to be validated separately. process (except in fluid bed granulation) not be overlooked.

n

granulation process was developed to handle powders of often widely different sizes. Such powders are often incompressible and impossible to handle without differences in particle size, shape, and moisture. Moisture specifications should be recorded, but often cannot be attained to the level required nor maintained in the interim. Tests would be required for finished granulation. Section guide [16] discusses this problem. Blending at the dry blend stage. Near uniformity typically require a specially sized granulation. It cannot be attained at the dry blend stage. The validation plan, and supported by tests to absolute uniformity. Most important, uniformity should be established in the protocol. The final validation plan, which finished tablets meet uniformity specifications within its uniformity specifications.

addresses various mixer types in the validation plan, and standards of practice. These are outlined in Table 5.

**Table 5** FDA-Recognized Mixer Limitations

Mixer type	Design feature	Limitations
Planetary (pony)	Open top	Cross-contamination
	Horizontal mixing	Poor top-to-bottom mixing
	Blade clearance	Poor mixing, segregation
Ribbon blender	Top loader	Cross-contamination (limited since blender closes during operation)
	Discharge valve	Dead spot
	Blade clearance	Poor mixing at ends of center bar and shell wall
Tumbler blender	Mixer volume	Overfill, poor mixing
	Shaft packings	Cross-contamination
	Mixer volume	Overfill, poor mixing
	Tumbling powders	Static lumping, low shear
High shear	High-energy input	Dissolve/recrystallization of drug
	Heat	Charring, melting
	Chopper	Cleaning

Source: Ref. 15.

Before any blending validation attempt, it is advisable to address these issues within the validation protocol.

Following the same logic, if the wet granulation process meets the goals of binding these physically different ingredients into a uniform granule, the finished granulation must meet final unit-of-use content uniformity specifications. The validation protocol should clearly state the expected uniformity requirements for the finished granulation.

## B. Drying

Two modes of drying are addressed in the FDA field manual [16]: tray and fluid bed dryers. Obviously, moisture uniformity is of paramount importance in validating a drying cycle. Tray dryers are inherently more prone to non-uniformity, owing to the static nature of the granule bed, and nonuniform tray loading. Tray loading should be addressed in the validation protocol.

Although less obvious in discussing dryers, FDA recognizes that fluid bed drying processes yield more uniform, spherical particles that are often more difficult to compress than similar products dried in static trays. Validation of the drying process cannot be considered complete until the differences in compression characteristics of granulations dried by the two processes are fully explored.



with other excipients (binders, particle size, shape, and distribution) nonsegregating granulation suited drying can alter the shape of particle size, but also the shape well-controlled milling process is effort.

ms was addressed by committee p of immediate-release products wise approach to scale-up, in-scale, components, and process- ee recommended that the signif- ical components be confirmed f the in vitro test had been cor- ent, the committee extended its d postapproval changes, in ad- to allow minor changes in non- d in Table 6. In any event, the

ponents

formula

drug substance/total excipient ratio should not change by more than 5%. Proof that a particular change in this category is indeed minor requires the manufacturer to demonstrate only that the product so manufactured continues to meet the final product specifications. Any quantitative change beyond the listed limits, other than removal of a color, should be considered a major change.

For components considered critical to the release mechanism (coating materials, matrix formers), the composition range should be justified in the application, based on its effects in an in vitro dissolution test which, in turn, is justified by an established in vitro—in vivo correlation.

The drug substance's physical specifications change on scale-up. The committee recognized the importance of changes in particle size, surface area, and intrinsic dissolution rate on control of drug release from the finished product. Citing as examples, a drug with 5 mg/mL or less aqueous solubility could tolerate no greater than a 10% change in any of these parameters as a minor change; a drug of higher solubility (> 5 mg/mL) could tolerate a 25% change in any of these. Changes outside these guidelines would be considered major, unless justified by appropriate scientific justification.

Unlike scale-up of immediate-release dosage forms, the guidance proposed at the 1992 FDA workshop clearly stated that no change in scale of individual unit operations is allowable for modified-release products. In the present case, this dictates that granulation, drying, blending, and compressing operations be fully scaled before pivotal pharmacokinetic testing. Process changes must be accompanied by full justification of the effect of changing all measurable variables on the final product. Any changes made must confirm that the product conforms to the same specifications using a biologically meaningful, predictive, and reliable dissolution test, and that the mechanism (i.e., diffusion or erosion) of drug release has not changed. A discussion of the dissolution test requirements for in vitro—in vivo correlation is beyond the scope of this text.

### E. Validation Requirements for the Preapproval Inspection

An FDA compliance policy guideline addresses process validation requirements for drug products subject to NDA or ANDA regulations [18]. FDA has also entered into the public record their interpretations of what is required at the preapproval inspection [19]. Although not a requirement for approval, process validation is a requirement for authorization to ship drug products for distribution. FDA recognizes that multiple batch validation may be cost prohibitive before approval and will grant conditional approval pend-

ing completion of appropriate validation efforts before any shipment. As a minimum, batch production records, component specifications and test methods, container closure source information, any contract manufacturer information, and all test results from the pivotal bioavailability and bioequivalence studies must be available.

If validation cannot be completed before the preapproval inspection, it is imperative that appropriate standard operation procedures (SOPs) are in place for validation at that time. A product-specific validation protocol, with proposed batch production records, should be available for inspection. In the event the multiple batch validation is impractical (e.g., an orphan drug with very limited distribution), the sponsor should be able to provide the following to a preapproval inspection team:

1. A clear documentation of the extenuating circumstances precluding preshipment validation.
2. A written commitment to following the validation protocol as written as time permits.
3. A commitment to conduct more extensive testing to ensure conformance to product specifications until validation can be completed.

The FDA has communicated through letters to manufacturers that, despite these minimal requirements, the agency expects the manufacturer to provide complete background information leading to the establishment of conditions and specifications for process validation. This information should be collected into a development summary report and should provide justification for the basic formulation and process.

## VI. SUMMARY

Establishment of global standards for the manufacturing, testing, documentation, and release of pharmaceuticals is progressing at an increasing rate. Already it is a virtual necessity for raw material and packaging component suppliers to list ISO 9000 certification among their credentials. ICH continues to publish guidelines that are accepted by regulatory authorities worldwide and promise to further harmonize manufacturing processes and both chemical laboratory and bioequivalence testing. Cooperative committee meetings between industry, academia, and regulatory authorities are establishing decision-making boundaries and reporting requirements that relinquish some of the FDA's preapproval requirements for minor process and formulation changes for certain classes of drug products. Regulatory guidelines specify GMP-like requirements for clinical supply manufacturing, and

mandate correlation with the validation holds the key to com

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## REFERENCES

1. Sampling and testing of 211.110. FOA.
2. Current Good Manufactur  
ments for finished pharma  
search, Rockville MD, M
3. ICH. Harmonized tripartit  
and products. ICH Steerin
4. SJ Romano, C Landsman,  
try: an overview. Pharm F
5. FDA. ISO Policy Implicat  
1993.
6. JP Skelly et al. Scaleup o  
Res 10(2), 1993.
7. FDA. Interim guidance, i  
post-approval changes: ch  
lution testing and in vivo  
Evaluation and Research,
8. FDA. Immediate release  
changes: chemistry, manu  
in vivo bioequivalence de  
uation and Research, Roc
9. FDA. Draft guidelines for  
New Drug Applications,  
drug products. Fed Reg 5
10. FDA guidance to industr  
annual report. As reprodu

efforts before any shipment. As a result, specific specifications and test methods for any contract manufacturer inform the regulatory process for bioavailability and bioequivalence.

Before the preapproval inspection, it is essential that granulation procedures (SOPs) are in place and a specific validation protocol, with all necessary data, be available for inspection. In some cases, this may be impractical (e.g., an orphan drug manufacturer should be able to provide the data).

Changing circumstances preclude

using the validation protocol as written.

Extensive testing to ensure consistency until validation can be completed.

Letters to manufacturers that, depending on the situation, expect the manufacturer to provide information leading to the establishment of a validation protocol. This information should be reported and should provide justification.

Manufacturing, testing, documentation, and packaging component testing are progressing at an increasing rate. ICH continues to update their credentials. ICH continues to work with regulatory authorities worldwide to harmonize manufacturing processes and both testing and documentation. Cooperative committee of regulatory authorities are establishing requirements that relate to minor process and product changes for drug products. Regulatory guidance for pharmaceutical supply manufacturing, and

mandate correlation with the final product intended for market. Process validation holds the key to confirming those correlations.

With these changes comes increasing responsibility for the formulation scientist and process engineer to further understand the effects of component and process alterations on the biological behavior of the new pharmaceutical product. Although some formulation and process changes are allowed without prior regulatory approval, all changes are limited in magnitude to those demonstrated to have no adverse product effects during validation. Periodic revalidation must be performed to demonstrate that the sum of minor changes made over time have not altered the original product characteristics. Only through intensive process validation efforts, necessitating a thorough understanding of the product, can the data package generated today possibly comply with these and impending regulatory requirements for new product approval.

## REFERENCES

1. Sampling and testing of in-process materials and drug products. 21CFR 211.110. FOA.
2. Current Good Manufacturing Practice; proposed amendment of certain requirements for finished pharmaceuticals. FDA Center for Drug Evaluation and Research, Rockville MD, May 3, 1996.
3. ICH. Harmonized tripartite guideline, stability testing on new drug substances and products. ICH Steering Committee, October 27, 1993.
4. SJ Romano, C Landsman, PJ Moran. ISO 9000 and the pharmaceutical industry: an overview. *Pharm Eng* 17, May/June 1994.
5. FDA. ISO Policy Implications for the FDA. Office of Policy, US FDA, January 1993.
6. JP Skelly et al. Scaleup of immediate release oral solid dosage forms. *Pharm Res* 10(2), 1993.
7. FDA. Interim guidance, immediate release solid oral dosage forms, pre- and post-approval changes: chemistry, manufacturing and controls, in vitro dissolution testing and in vivo bioequivalence documentation. FDA Center for Drug Evaluation and Research, Rockville MD, November 29, 1994.
8. FDA. Immediate release solid oral dosage forms, scale-up and post-approval changes: chemistry, manufacturing and controls, in vitro dissolution testing and in vivo bioequivalence documentation, guidance. FDA Center for Drug Evaluation and Research, Rockville MD, November 30, 1995.
9. FDA. Draft guidelines for supplements to New Drug Applications, Abbreviated New Drug Applications, or Abbreviated Antibiotic Applications for nonsterile drug products. *Fed Reg* 59(237), Dec. 12, 1994.
10. FDA guidance to industry: format and content for the CMC section of an annual report. As reproduced in *The Gold Sheet*, 29(2):8-12, February 1995.

11. LJ Lucisano, RM Franz. FDA proposed guidance for chemistry, manufacturing, and control changes for immediate-release solid dosage forms: a review and industrial perspective. *Pharm Technol* May: 30–54, 1995.
12. Current Good Manufacturing Practice for finished pharmaceuticals. 21CFR part 211, 1978.
13. FDA. Guideline on the preparation of Investigational New Drug products (human and animal). FDA Center for Drug Evaluation and Research, March 1991.
14. Control of components and drug product containers and closures. 21CFR 211, Subpart E, 1978.
15. Component, drug product container, closure and labeling records. 21CFR 211.184.
16. FDA. Guide to inspections of oral solid dosage forms pre/post approval issues for development and validation. FDA, Jan 1994.
17. JP Skelly et al. Scaleup of oral extended release dosage forms. *Pharm Res* 10(12), 1993.
18. FDA. Process validation requirements for drug products subject to pre-market approval compliance policy guides 7132c.08 and 7125.38. FDA Office of Enforcement/Division of Compliance Policy, issued 8/30/93.
19. FDA. New Drug and Abbreviated New Applications: preapproval inspection requirements. *Fed Reg* 58(172), September 8, 1993.

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